The impact of vaccination on adenocarcinoma associated with non-vaccine type HPV: a mathematical model with two HPV types

Master's Thesis

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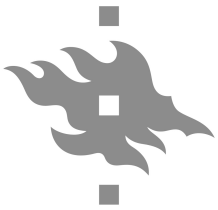

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The human papilloma virus (HPV) is the main cause of cervical cancer in women and HPV is the most common sexually transmitted infection. To prevent women from developing cervical cancer there are two methods in use, the primary method being vaccination against HPV and the secondary being screening. Some long term effects of screening and vaccination will not be observed during the first decades of vaccination, and therefore predictive mathematical models serve as an indicator of what to anticipate in the future. In this thesis we studied two types of cervical cancer, adenocarcinoma and squamous cell carcinoma. We determined how vaccination against a virus, associated with squamous cell carcinoma, together with screening programs affects adenocarcinomas caused by non-vaccine type HPV.

A precancerous adenocarcinoma lesion, which is located deeper in the glandular cervical tissue, is difficult to detect directly in screening but can be found indirectly by uncovering a common type of cervical cancer, squamous cell carcinoma, which is easier to detect in screening. These two cancers are mostly associated with two different strains of HPV. When vaccinating against the strain that is found in squamous cell carcinomas the elimination of the precancerous stages of squamous cell carcinomas mean that the detection method for adenocarcinoma is impaired, which allows for a possible increase in adenocarcinoma prevalence. In this thesis we studied this possible increase.

To predict the effect vaccination has on adenocarcinoma, we constructed a mathematical model of two HPV types, which were associated with squamous cell carcinoma and adenocarcinoma respectively. We modeled a vaccine that protects against the HPV types associated with squamous cell carcinoma but not adenocarcinoma. The model included the simplified natural history of HPV, the progression of the disease, the vaccination program and the screening program. For the two virus infections we developed a deterministic compartmental progression model. In the computations we modeled a cohort of women through their lifetime and studied the precancerous findings in screenings and the number of cancer cases in the cohort. To understand which model components contributed to the adenocarcinoma incidence a sensitivity analysis was conducted by varying the screening sensitivity, the force of infection and the recovery rates.

The model yielded an increase in adenocarcinomas when vaccinating against the virus associated with squamous cell carcinoma. The incidence of adenocarcinoma correlated with the non-vaccine type HPV infections that would otherwise be found in screenings without vaccination. The increase in adenocarcinomas was more prominent in a sexually active population. Compared to the reduction in squamous cell carcinoma provided by the vaccine, the adenocarcinoma increase was, although positive, very minor.

Avainsanat — Nyckelord — Keywords
Human papilloma virus, vaccination, screening, cervical cancer, adenocarcinoma, progression model

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Contents

Chapter 1

Introduction

The human papilloma virus (HPV) is the main cause of cervical cancer in women [1]. HPV is the most common sexually transmitted disease and most men and women are infected by HPV during their lifetime [2]. To prevent women from developing cervical cancer there are two intervention methods in use. The primary intervention is vaccination of pre-adolescent girls against the most oncogenic HPV types and the secondary is screening through Pap- or HPV-DNA tests by which lesions are detected and treated already at a precancerous stage.

The most common type of cervical cancer is squamous cell carcinoma, which accounts for 70% of all cervical cancers [3] and is located in mucous membrane. A less common type of cervical cancer is adenocarcinoma, which is located in deeper glandular tissue and accounts for approximately 10% of all cervical cancers [3]. The Pap test is a smear test which can detect abnormal cells, indicating potential cervical cancer with moderate sensitivity and specificity. If a smear test is positive a sample of the tissue, known as a biopsy, is taken to confirm a carcinoma finding. Because of the adenocarcinoma location deeper in the glandular tissue, the adenocarcinoma lesions are more difficult to detect in screening than squamous cell carcinomas [4]. Analyzing the biopsy can reveal an underlying adenocarcinoma located deeper in the tissue. Because of this difficulty to detect adenocarcinoma in screening, it is rarely detected alone and usually found by first detecting a squamous cell carcinoma nearby [5]. This means that the detection of adenocarcinomas largely depend on the detection of squamous cell carcinomas.

Of the over 100 HPV types the most oncogenic ones are HPV 16 and 18, which cause approximately 70% of all cervical cancers [2, 3]. Squamous cell carcinoma is mostly caused by HPV 16, followed by HPV 18 and HPV 45 [3]. The HPV types found in adenocarcinomas are largely the same as in squamous cell carcinomas, but the proportion of HPV 18 and HPV 45 infections is greater in adenocarcinomas than in squamous cell carcinoma.

There are three prophylactic HPV vaccines on the market [6], a bivalent, a quadrivalent and a nonavalent vaccine. The bivalent vaccine contains virus-like particles of HPV 16 and 18, and therefore it protects against these. The quadrivalent vaccine contains virus-like particles of HPV 16, 18 as well as the non-oncogenic types 6 and 11 and provides a protection against all these types. The third vaccine is a nonavalent vaccine protecting against nine HPV types, including HPV 16, 18 and 45. The nonavalent vaccine is relatively new and will be replacing the quadrivalent vaccine. All the vaccines may protect against other HPV-types too by cross protection. The bivalent and quadrivalent vaccines have been in use in many countries approximately a decade, while the nonavalent was approved in Europe in 2015. The bivalent vaccine provides cross protection against HPV 45 while the quadrivalent vaccine does not [7]. This means that when vaccinating with the quadrivalent vaccine, there is no protection against HPV 45 and adenocarcinomas caused by this virus can continue to develop despite the vaccination.

If the squamous cell carcinomas are largely eliminated as a result of vaccination with the quadrivalent vaccine, the number of detected precancerous stages of adenocarcinoma can decrease as a result of this. The adenocarcinomas that have been detected after uncovering a squamous cell carcinoma in the pre-vaccination era will not be noticed when a population is vaccinated. Therefore the number of adenocarcinomas could increase as a result of vaccination with the quadrivalent vaccine combined with a screening program. This raises the question about whether elimination of HPV 16 and 18 without cross protection against HPV 45 will affect the number of adenocarcinomas caused by HPV 45. The strains would not compete, but elimination of HPV 16 and 18 could lead to an increase in adenocarcinomas, which also would be the case if HPV 45 replaced HPV 16 and HPV 18.

The aim of this research is to investigate if and how the number of adenocarcinomas

are affected by vaccinating a population that is also screened regularly. The aim is also to understand how the population characteristics, such as sexual activity, as well as virus traits, such as recovery, and screening sensitivity affect a possible increase in adenocarcinomas. Will the vaccination result in an increase in cancers caused by a virus that is not eliminated through vaccination and should we be concerned about this?

To answer the questions above we construct two artificial HPV-types corresponding to HPV 16 and 45, which are developed to determine the characteristics of the phenomena. We develop a deterministic Markov process model to run the natural history of the two strains and include a screening program in the model. These procedures are applied from S. Vänskä et al [8]. We model a homogeneous age-cohort of women and compute the number of infections, precancerous findings and cancers at each age. We perform sensitivity analysis to get insight in how parameters contribute to the adenocarcinoma prevalence. We wish to draw conclusions about type replacement in this simplified setting, which could indicate what to expect in real life.

HPV vaccination programs have been in use for about a decade, and some long term impacts have not occurred yet. Mathematical models are widely used to predict long term outcomes and HPV has been modeled extensively during the last decades. An overview of the consistency of mathematical models has been done by M. Brisson et al. [9], who conclude that even though HPV models with vaccination vary in structure, the predictions they make are consistent. The effects of a possible screening-vaccination induced adenocarcinoma increase will not be observed clinically in many years yet, which allows for mathematical modeling as a unique method to anticipate the prospect of type replacement. To our knowledge there is no published work studying this specific screening-vaccination induced adenocarcinoma increase, although type replacement relating to HPV has been modeled by for example J. E. Tota et al [10].

Even though we model the vaccination program in this thesis, this is neither a comparison of the two available vaccines nor is it a study in vaccine efficacy or effectiveness. The vaccine and vaccination programs are already thoroughly studied in the scientific community [11, 12].

Chapter 2

HPV, cervical cancer and interventions

2.1 HPV and cervical cancer

Cancer means that cells and tissues grow uncontrollably. Cancer cells can develop into tumors and invade new tissues destroying healthy tissue when competing for resources. Cervical cancer is mostly caused by a long lasting HPV-infection [2]. In 93% of cervical cancer tumor findings there is detected HPV DNA [3] and the causality of HPV leading to cervical cancer is well known and thoroughly studied [1].

Cervical cancer is the second most common cancer in the developing world, while western Europe has had lower incidence rates since the introduction of screening programs [4]. Cervical cancer is the fourth most common cancer and third leading cause of cancer-related death among Finnish women aged 15 to 44 [13]. Worldwide the cervical cancer prevalence varies highly depending on region and continent and the highest mortality rates are in Africa and Melanesia, while Western Europe, Western Asia and Northern Africa have much lower mortality rates [14].

The HPV virus transmits through sexual contact and almost all women and men get infected by some HPV type during their lifetime [2]. In most cases HPV infections go unnoticed since 95% of the infections clear in two years [15] and do not cause any detectable symptoms. The HPV incidence, the number of new HPV infections over time,

depends on sexual activity [16]. The sexual activity in turn depends on the age structure, culture as well as many other factors, and therefore the population characteristics also have an impact on the spread of HPV. Some of the HPV types found in genitalia are less harmful and these are known as low risk HPV and typically cause genital warts. The oncogenic HPV types are known as high risk HPV types and can cause abnormalities and cancers in cervical tissue.

When infected with HPV, the infection is usually cleared by the immune system [15]. If a high risk HPV infection persists, there is a risk of developing cell abnormalities and precancerous lesions, known as neoplasms. Some of the neoplasms clear spontaneously, while others persist. If a neoplasia is of squamous cell carcinoma type, it is known as a cervical intraepithelial neoplasia (CIN), and if it is an adenocarcinoma neoplasia, it is known as a cervical glandular intraepithelial neoplasia (CGIN). The neoplasms can evolve and become cancers, but also regress and clear spontaneously. The squamous cell carcinoma is located in the mucous membrane of the cervix, while adenocarcinoma develops deeper in the glandular tissue. For a schematic outline of the location of the carcinomas, see Figure 2.2.

The oncogenic HPV types in cervical cancers are well known and it is also known that different cancer types have different virus-type distributions. The HPV 16 virus is found in 61% of all invasive cervical cancers (in 62% of squamous cell cancers and in 50% of adenocarcinomas), HPV 18 is found in 10% of all invasive cancers (in 8% of squamous cell cancers and in 32% of adenocarcinomas) and HPV 45 is found in 6% of all invasive cancers (in 5% of squamous cell cancers and in 12% of adenocarcinomas) [3], see Figure 2.1.

2.2 Vaccination

Over a third of the countries in the world (71 countries) use vaccination as the primary method to protect against cervical cancer [6]. In addition to the earlier bivalent and quadrivalent vaccines, the fairly new nonavalent vaccine was approved in Europe in 2015 [18]. The vaccination program in Finland included HPV vaccination in 2013 [19] and the World Health Organization (WHO) recommends vaccination against HPV as a primary intervention [2]. The vaccine efficacy being over 90% for both the bivalent and quadriva-

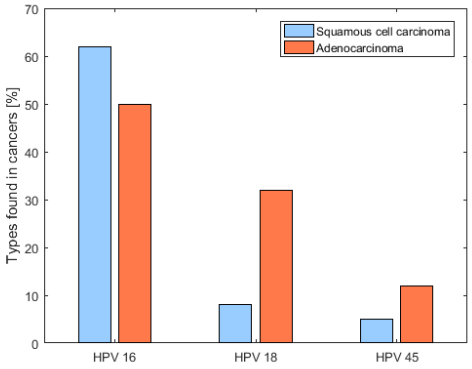

Figure 2.1: The HPV type representation in squamous cell carcinomas and adenocarcinomas, values from [3].

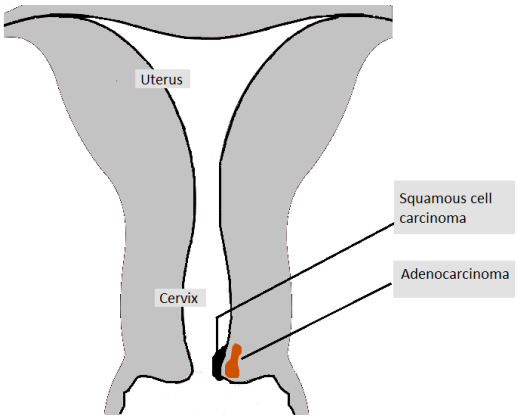

Figure 2.2: Schematic view of the relative location of a squamous cell carcinoma and an adenocarcinoma. Adapted from [17].

lent vaccine [20, 21], the vaccine prevents from most HPV-infections of the targeted types and from developing precancerous lesions. Vaccination is recommended before initiation of sexual activity, since the vaccine is not offering protection against already existing infections.

Vaccines can provide cross protection against other virus types than the targeted types. Cross protection against HPV 31, 33 and 45 is high in the bivalent vaccine and lower in the quadrivalent vaccine [7]. The bivalent vaccine provides cross-protection against HPV 45 infection with high efficacy (approximately 80%) and the quadrivalent vaccine with close to zero efficacy. There is full cross protection for HPV 45 precancerous stage with the bivalent vaccine and no protection with the quadrivalent one [7].

2.3 Screening

Screening is used as a secondary intervention to prevent HPV infections from progressing to precancerous stages and invasive cervical cancer. The screening program in Finland starts at age 30 and ends at age 60, and the invitations to screening come at 5 year intervals, but there is additional opportunistic screening conducted at more frequent intervals independently of the national program [22]. In the western world (Europe and US) the intervals between screening rounds normally range between 1 and 5 years [23]. A screening

program with treatment options and screening rounds every 3-5 years reduces the cancer incidence significantly [2].

The Pap test was invented by the Greek scientist Georgios Papanikolaou and it is a cytological test, while the DNA test detects HPV genes and is a primary test with Pap triage. An abnormal Pap test is usually followed up by a colposcopy or biopsy to confirm the finding [2]. The Pap test detects squamous cell carcinomas well, but is less efficient in detecting adenocarcinomas [4]. As stated in chapter 1 the adenocarcinomas are mainly found in connection with squamous cell carcinoma findings [5].

2.4 Type replacement

Viruses, and pathogens in general, respond to the environment and can evolve in order to survive. When a common virus type is replaced by a rarer virus type, it is called type replacement [24]. HPV strains are stable and the mutation rate is low, as opposed to e.g. penumonia, making genotype replacement unlikely [10]. When vaccines are introduced in a population, some non-vaccine virus types can increase in the host as a consequence of vaccination. If the type replacement is caused by a vaccine, it is known as vaccine-induced pathogen strain replacement, a well-known phenomenon observed for example when vaccinating against pneumonia (Streptococcus pneumonie), influenza (Haemophilus influenzae), meningococcus (Neisseria meningitidis) and pertussis (Bordetella pertussis) [24].

The type replacement can also be caused by other mechanisms than vaccination. Type replacement should not be confused with unmasking, which means that there is a falsely assumed causality between a virus strain and a cancer type. The mechanism of screening- and vaccination-induced adenocarcinoma increase that is researched in this thesis is not strictly speaking type replacement, since the elimination of one virus type resulting in an increase in another virus type related cancer would not be type replacement. Although the "man made" mechanism implied in this thesis is not precisely biological type replacement, it resembles type replacement closely.

The vaccines against HPV have not been in national vaccine programs for a long time and therefore no unambiguous conclusions about type replacement have been made yet

[25]. Cross-protection could in theory prevent from type replacement, but the discussion about whether cross protection prevents type replacement is heated in the scientific community [26, 27] and further investigation is needed to clarify the matter.

2.5 The research question in detail

The question we aim to answer is how the number of adenocarcinomas change as a consequence of vaccination and screening. More precisely, will reducing the ability to detect CGIN, because of vaccination and elimination of the squamous cell carcinomas, lead to a significant increase in adenocarcinomas? Can we notice a phenomenon resembling type-replacement, where the elimination of one virus strain allows for an increase in cancers caused by another strain?

In addition to computing the change in adenocarcinomas, we will also assess the impact different population and virus characteristics have on the number of adenocarcinomas. We will study if there are certain conditions that amplify a change in adenocarcinoma incidence. We are also interested in determining if there are limit or maximal values that affect the number of adenocarcinomas. Therefore we aim to determine which virus traits or which interventions affect the number of adenocarcinomas most and how substantial the impact is on adenocarcinoma prevalence. To assess how sexual behavior affects the number of HPV infections, precancers and cancers respectively we will compute results with different sexual activities. We also aim to understand how different screening intervals affect the number of adenocarcinomas and if these intervals have an impact on the findings.

Chapter 3

Methods

To compute how the number of adenocarcinomas are affected by screening and vaccination, we developed a compartmental deterministic model for cervical cancer progression and interventions. We model the progression of a cohort of women through their lifetime and collect the number of screening findings and cancers that appeared during the lifetime of the cohort. The cohort enters the model at a certain age, may or may not be vaccinated, progresses in time, participates in screening and we study how many individuals are in each disease state.

The natural history of the HPV virus was discretized and simplified to capture the crucial aspects of disease progression, screening and vaccination. Studying the effects of the input values was also an important aspect and it was essential to have the possibility to vary inputs and easily run the model with a range of values in order to determine if there were certain conditions that amplified a change in adenocarcinoma incidence.

To understand how the number of cancers caused by two different HPV viruses changed with vaccination and screening, the model included two theoretical HPV types, HPV_{SCC} and HPV_{ADC}. In the model HPV_{SCC} was assumed to be a virus causing squamous cell carcinomas and HPV_{ADC} was assumed to be a virus causing adenocarcinomas. The vaccine in our model is assumed to fully protect against HPV_{SCC} but not against HPV_{ADC}, and does not provide any cross protection against HPV_{ADC} either. Screening aside, the natural histories of the two virus types were assumed independent of each other.

The reason why we use a numerical progression model instead of analyzing possible

equilibria and stabilities of these is that the time line in reaching equilibriums might be very long, while this study is a study of the effects of interventions in public health in the near future. Population equilibria are not the most accurate description in this setting because of the introduction of new vaccines with new properties replacing the older vaccines. The discontinuity of screening is also problematic when modeling populations analytically.

3.1 The model

3.1.1 Natural history

In the model we consider population level dynamics. This means that the focus is not on an individual alone but on the population as a homogeneous group where the same rates apply to all individuals. Individuals are grouped into states according to their disease stage and proceeded from one state to another according to the outline in this section.

Consider an infection of a single-type of squamous cell carcinoma virus HPV_{SCC}. We define the state space to be

$$X = \{S, I, CIN, SCC, R, V\}$$

where S stands for susceptible, I stands for infection that has not progressed to neoplasia, CIN stands for cervical intraepithelial neoplasia (the precancerous state), SCC stands for squamous cell carcinoma, R stands for recovered and immune and V stands for immunized-by-vaccination. The states in the state space are also referred to as the disease states.

For the adenocarcinoma virus HPV_{ADC} the state space is

$$Y = \{S, I, CGIN, ADC, R, V\},$$

where CGIN stands for cervical glandular intraepithelial neoplasia and ADC for adenocarcinoma, and the rest of the states are equivalent with the HPV_{SCC} states.

The rates, or expected number of transitioning individuals between compartments per unit of time, are indicated by arrows in Figure 3.1 and Figure 3.2 and summarized in

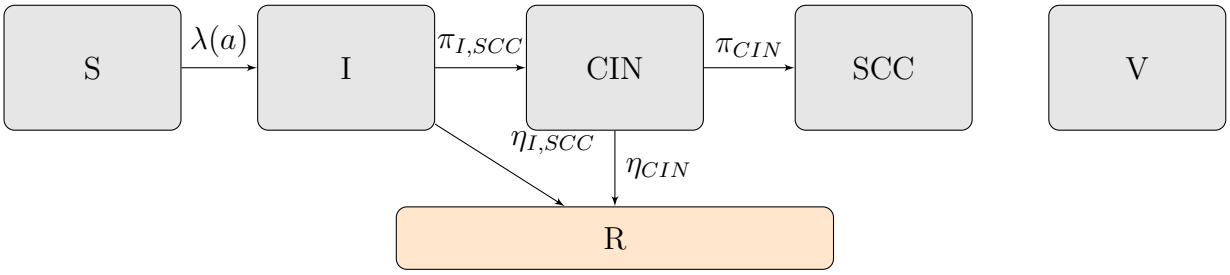

Figure 3.1: Compartmental flow chart of a HPV_{SCC} infection.

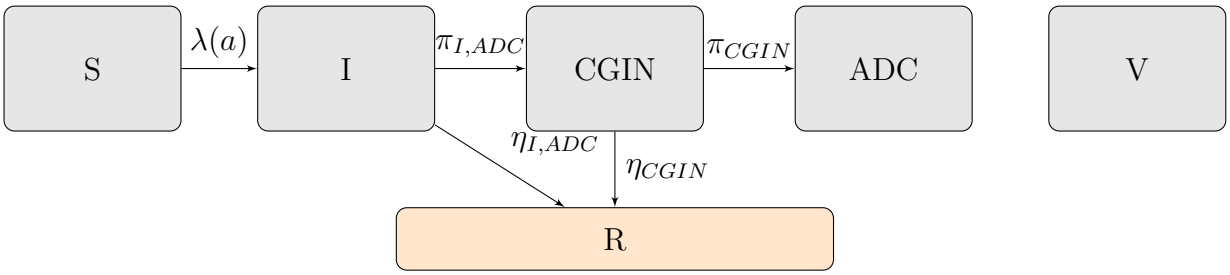

Figure 3.2: Compartmental flow chart of a HPV_{ADC} infection.

Table 3.1. All the rates are type specific. Recovery is possible from the I, CIN and CGIN states, whereas the SCC and ADC states are absorbing states and the V state is an isolated state. We do not take background death into count in this model. See figures 3.1 and 3.2 for schematic descriptions of the natural history.

The transition from S to I is known as the force of infection. The model does not take into count transmission dynamics but has HPV infection rate as a model input. To model the force of infection λ we use an age dependent, HPV-like function, first presented in [8]. The value of λ at age a is

$$\lambda(a) = \frac{K}{c}(a - a_0)^{\kappa} e^{-(a-a_0)/\theta} + 0.05K \tag{3.1}$$

where

$$\kappa = (a_M - a_0)/\theta \text{ and } c = (\kappa\theta)^{\kappa} e^{-\kappa}$$

and a_0 is the entering age, K is the maximal force of infection value, a_M is the age at this

Rate	Description
$\lambda(a)$	Force of infection, age dependent
π_I	Progression rate
π_{CIN}	Symptom rate in CIN
π_{CGIN}	Symptom rate in CGIN
η_I	Clearance rate from I
η_{CIN}	Clearance rate from CIN
η_{CGIN}	Clearance rate from CGIN

Table 3.1: Transition rates.

maximum and θ is the tail thickness. The progression rate from I to CIN is $\pi_{I,SCC}$, the progression rate from I to CGIN is $\pi_{I,ADC}$, the progression from CIN to SCC is π_{CIN} and from CGIN to ADC is π_{CGIN}. Clearance, also known as recovery, from I is determined by η_I, from CIN by η_{CIN} and from CGIN by η_{CGIN}. We assumed that an infection with a HPV type implies a life long immunity to it, which means that the R-state is a terminal state. If a population is vaccinated, the vaccination is conducted before the entering age a_0 which means that they are in the V-state at a_0. The immunity from vaccination was also assumed lasting life long, which in turn explains why the V-state is an isolated state. The natural history parameters, such as progression and recovery from the disease, were assumed to be independent of age.

The differential equation system describing the HPV_{SCC} model is

$$\begin{cases} \dot{S} & = -\lambda(a)S \\ \dot{I} & = \lambda(a)S - \pi_I I - \eta_I I \\ \dot{CIN} & = \pi_I I - \pi_{CIN} CIN - \eta_{CIN} CIN \\ \dot{SCC} & = \pi_{CIN} CIN \\ \dot{R} & = \eta_I I + \eta_{CIN} CIN \\ \dot{V} & = 0 \end{cases} \tag{3.2}$$

with the initial value

$$\begin{cases} S(0) & = 1 \\ I(0) & = 0 \\ CIN(0) & = 0 \\ SCC(0) & = 0 \\ R(0) & = 0 \\ V(0) & = 0 \end{cases}$$

for a non-vaccinated population and

$$\begin{cases} S(0) & = 0 \\ I(0) & = 0 \\ CIN(0) & = 0 \\ SCC(0) & = 0 \\ R(0) & = 0 \\ V(0) & = 1 \end{cases}$$

for a vaccinated population. The differential equation system for $\mathrm{HPV}_{\mathrm{ADC}}$ is analogously

$$\begin{cases} \dot{S} & = -\lambda(a)S \\ \dot{I} & = \lambda(a)S - \pi_I I - \eta_I I \\ \dot{CGIN} & = \pi_I I - \pi_{CGIN} CGIN - \eta_{CGIN} CGIN \\ \dot{ADC} & = \pi_{CGIN} CGIN \\ \dot{R} & = \eta_I I + \eta_{CGIN} CGIN \\ \dot{V} & = 0 \end{cases} \tag{3.3}$$

with the initial value

$$\begin{cases} S(0) & = 1 \\ I(0) & = 0 \\ CGIN(0) & = 0 \\ ADC(0) & = 0 \\ R(0) & = 0 \\ V(0) & = 0 \end{cases}.$$

For this system the initial value for no vaccination does not differ from vaccination, because HPV_{ADC} is not a vaccine type. In Equation 3.3 the V-state is redundant, and could be left out of the equation. Although redundant, we keep the V-state in the notation for the sake of symmetry in the two-type virus case described below.

When modeling a co-infection, where an individual can be infected with HPV_{SCC} and HPV_{ADC} simultaneously, the state space is $X \times Y$ with states $(x, y) \in X \times Y$ where x is the disease state of HPV_{SCC} and y is the disease state of HPV_{ADC}. There are now 36 possible HPV states in the two type state space. The co-infection model follows the idea of the single-type model, but with type-specific rates λ_i, $\pi_{I,i}$, ρ_i, η_{Ii}, π_{CIN}, π_{CGIN}, η_{CIN} and η_{CGIN} where $i = SCC, ADC$. For the co-infection model the transitions between the disease states are determined by Equation 3.2 and Equation 3.3.

3.1.2 Time handling

The time unit in the model is one year, and all rates were defined according to this. To propagate a cohort of women in time, we defined the time step to be $\Delta t = 1/52$, one week. Time started at the model entering age a_0, which was 10 in our simulation, and ended at age a_n, which was 70 in our simulation. Between these ages we moved one Δt forward in time, propagating the cohort one week and updating it accordingly. In the simulation, age and time coincide, so as we propagated our cohort in time, the cohort aged according to the same time step length. A possible vaccination was conducted before a_0 and the schematic idea of the time progression is sketched in Figure 3.3.

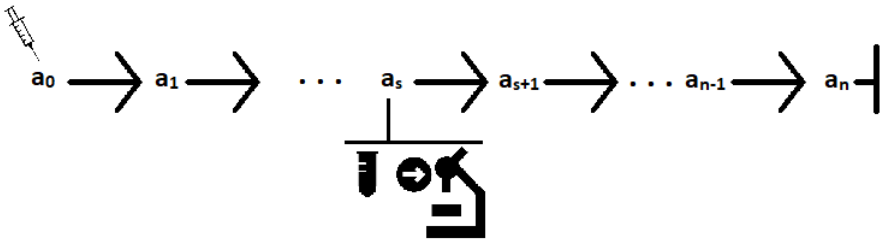

Figure 3.3: Time progression in the model, where a_0 is the entering age, before which a possible vaccine is taken, a_s is a screening age and a_n is the exit age.

3.1.3 Transition probability matrix and updating the cohort

Suppose a cohort of women has a certain distribution on the disease states. To propagate it one step in time, we need a matrix that gives the transition probabilities for that time step. The process in time is a Markov chain, where the next state in time is determined only by the current state, see Appendix B for more detailed descriptions.

Denote a two-type disease distribution by F where $F = F((x, y); a)$ is a discrete probability distribution function describing the distribution on the disease states. For simplicity, consider first a single type disease distribution F_1 where $F_1 = F_1(x; a)$ is a distribution on X. In order to propagate a single-type population F_1 in time from t to $t + \Delta t$, we compute the probability of changing state from $x' \in X$ to $x \in X$ with the number of individuals in $F_1(x'; t)$ and then sum up all the transitions to this state.

Let x and x' be states in X and let $q(x, x'; t)$ be the rate from x' to x at time t, where the rate may depend on the time t, especially the force of infection in this model. For the sake of simplicity we leave out the t-notation and denote the rate by $q(x, x')$. Denote the sum of the rates out from state x' by

$$\tilde{q}(x') = \sum_{x \in X} q(x, x'). \tag{3.4}$$

The probability $P_x(\tau)$ of still being in state x at τ time provided that $P_x(0) = 1$ is

$$\frac{dP_x(\tau)}{d\tau} = -\tilde{q}(x)P_x(\tau)$$

and solving this ODE gives

$$P_x(\tau) = P_x(0)e^{-\tilde{q}(x)\tau} = e^{-\tilde{q}(x)\tau}. \tag{3.5}$$

From Equation 3.5 we get the probability of remaining in state x at time $t+\Delta t$, given that we are in state x at time t, as $e^{-\tilde{q}(x)\Delta t}$. The probability of transitioning out from state x, which is the probability of not remaining in state x at time $t + \Delta t$, given that we are in state x at time t, is therefore $1 - e^{-\tilde{q}(x)\Delta t}$. Note also that the probability of transitioning specifically from x' to x in Δt is

$$\frac{P(x' \text{ to } x)}{P(\text{any transition from } x')} = \frac{q(x,x')\Delta t}{\tilde{q}(x')\Delta t} = \frac{q(x,x')}{\tilde{q}(x')}.$$

By combining these observations we can conclude that the probability of remaining in a state, and the probability of a specific transition, can be summarized with the transition probability function

$$N_{\Delta t}(x,x';t) = \begin{cases} e^{-\tilde{q}(x')\Delta t} & \text{if } x' = x \\ (1 - e^{-\tilde{q}(x')\Delta t})\frac{q(x,x')}{\tilde{q}(x')} & \text{if } x' \neq x \text{ and } \tilde{q}(x') \neq 0 \\ 0 & \text{if } x' \neq x \text{ and } \tilde{q}(x') = 0, \end{cases} \tag{3.6}$$

where $N_{\Delta t}$ is dependent on the size of the time step Δt and also on the current time t, because of the force of infection being time-dependent. Note that the columns of $N_{\Delta t}$ have to sum up to 1 to meet the constraints of a transition probability matrix. Updating the whole cohort one time step is therefore

$$F_1(x; t + \Delta t) = \sum_{x' \in X} N_{\Delta t}((x,x');t)F_1(x';t). \tag{3.7}$$

or simply $F_1(t + \Delta t) = N_{\Delta t}F_1(t)$, where $N_{\Delta t}$ is the transition probability function, also

known as the natural history function.

Propagating a two-type cohort matrix F is similar to the one described by Equation 3.7, but now we have two progression matrices $N_{\Delta t}^{SCC}$ and $N_{\Delta t}^{ADC}$. The assumption that the two virus types are independent in their progression between states means that updating the cohorts can be done by two progression matrices,

$$N_{\Delta t}^{SCC}((x,x');t) = \begin{cases} e^{-\tilde{q}_{SCC}(x')\Delta t} & \text{if } x' = x \\ (1-e^{-q_{SCC}(x')\Delta t})\frac{q_{SCC}(x,x')}{\tilde{q}_{SCC}(x')} & \text{if } x' \neq x \text{ if } x' \neq x \text{ and } \tilde{q}(x') \neq 0 \\ 0 & \text{if } x' \neq x \text{ and } \tilde{q}_{SCC}(x') = 0 \end{cases} \tag{3.8}$$

and

$$N_{\Delta t}^{ADC}((y,y');t) = \begin{cases} e^{-\tilde{q}_{ADC}(y')\Delta t} & \text{if } y' = y \\ (1-e^{-q_{ADC}(y')\Delta t})\frac{q_{ADC}(y,y')}{\tilde{q}_{ADC}(y')} & \text{if } y' \neq y \text{ if } y' \neq y \text{ and } \tilde{q}(y') \neq 0 \\ 0 & \text{if } y' \neq y \text{ and } \tilde{q}_{ADC}(y') = 0 \end{cases} \tag{3.9}$$

with the type-specific rates q_{SCC} and q_{ADC}, and with $x, x' \in X$ and $y, y' \in Y$. Perturbing a two-type distribution with Δt follows exactly the same idea as in equation Equation 3.7. Applying Equation 3.7 on both HPV types gives $F_{SCC}(t+\Delta t) = N_{\Delta t}^{SCC} F_{SCC}(t)$ and $F_{ADC}(t+\Delta t) = N_{\Delta t}^{ADC} F_{ADC}(t)$ and with the two-type distribution $F = F_{SCC} F_{ACD}^T$ it yields

$$\begin{aligned} F_{SCC}(t+\Delta t)F_{ADC}(t+\Delta t)^T &= (N_{\Delta t}^{SCC} F_{SCC}(t))(N_{\Delta t}^{ADC} F_{ADC}(t))^T \\ &= N_{\Delta t}^{SCC} F_{SCC}(t) F_{ADC}(t)^T (N_{\Delta t}^{ADC})^T \\ &= N_{\Delta t}^{SCC} F(t) (N_{\Delta t}^{ADC})^T \end{aligned}$$

which gives

$$F(t+\Delta t) = N_{\Delta t}^{SCC} F(t) (N_{\Delta t}^{ADC})^T. \tag{3.10}$$

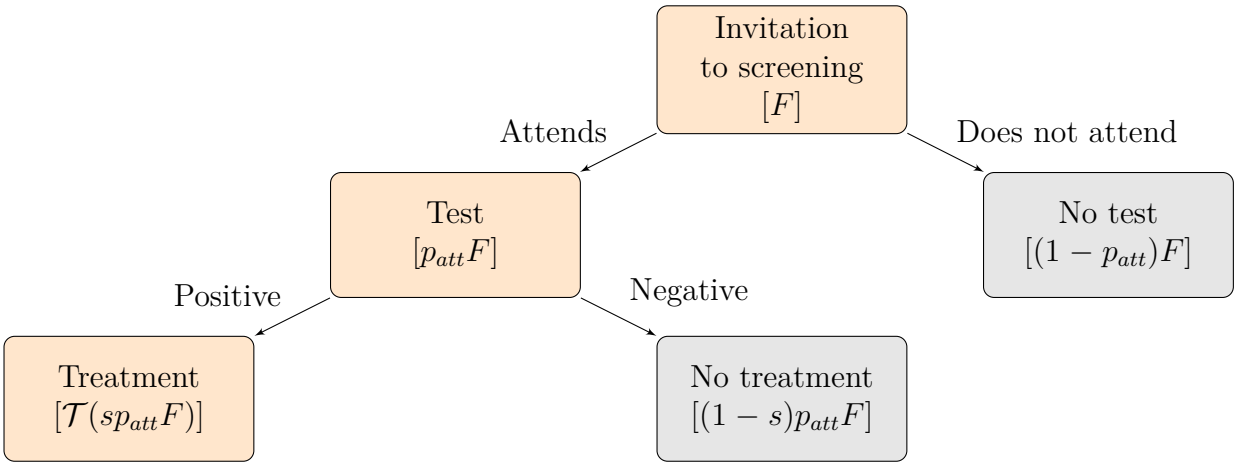

Figure 3.4: Screening scheme. F is the population, p_{att} is the attendance probability and s is the screening sensitivity.

3.1.4 Screening

When a woman is at a screening age, she attends screening with a certain probability. Let the screening ages be a set of pre-determined ages,

$$A_s = \{a_{s1}, a_{s2}, \ldots, a_{sn}\}.$$

The screening scheme implemented in our model is presented in Figure 3.4. The probability of an individual attending a screening is denoted by $p_{att} \in [0, 1]$ and we assumed that the probability of attending screening is independent of age. A woman attending screening goes through a screening test and if she has developed a neoplasia, the test shows it with a state-dependent sensitivity $s_{SCC}(x) \in [0, 1]$, $x \in X$ for HPV_{SCC} and $s_{ADC}(y) \in [0, 1]$, $y \in Y$ for HPV_{ADC}. For a co-infection with HPV_{SCC} and HPV_{ADC} the sensitivity in state (x, y) is determined by

$$s(x, y) = 1 - (1 - s_{SCC}(x))(1 - s_{ADC}(y)) \text{ where } x \in X \text{ and } y \in Y, \tag{3.11}$$

where s_{SCC} and s_{ADC} are the screening sensitivities for the types x and y alone.

In the model, only the CIN- and CGIN-state individuals are detected in screening. The I-state infection is not yet detected in tests and the C-state is considered a symptomatic state, which means that it is detected by symptoms and treated outside the screening program. Upon detection of a positive result the individual is treated and becomes immune.

Consider the disease distribution $F(\cdot; a)$. If it is at a screening age, i.e. if $a \in A_s$, it undergoes screening. The probability of attending was p_{att}, therefore the distribution is divided into two sub-distributions, the attendants and non-attendants, $p_{att}F$ and $(1 - p_{att})F$. Each disease state $p_{att}F$ undergoes treatment with the screening sensitivity s determined by Equation 3.1.4. Therefore the sub-distribution $p_{att}F$ gets further divided into two sub-sub-distributions, one with positive test results $sp_{att}F$ and one with negative test results $(1 - s)p_{att}F$. Let the matrix $T := sp_{att}F$ denote the findings, i.e. the positive results. The distribution of the findings, i.e. the number of individuals with CIN, CGIN, both, or one precancer and one infection, are collected and stored in the T-matrix at each screening. The individuals that test positive undergo treatment, where the treatment is defined for every entry T with the treatment function

(3.12)

$$(\mathcal{T}T)(x,y) = \begin{cases} T(x,y) + T(CIN,y), & \text{if } x = R \text{ and } y \neq I \text{ and } y \neq CGIN \\ T(x,y) + T(x,CGIN), & \text{if } y = R \text{ and } x \neq I \text{ and } x \neq CIN \\ T(x,y) + T(CIN,CGIN) & \\ \quad + T(I,CGIN) + T(CIN,I), & \text{if } y = R \text{ and } x = R \\ 0, & \text{if } x = CIN \text{ or } y = CGIN \\ T(x,y), & \text{otherwise} \end{cases}$$

where infections also get treated when a CIN or CGIN neoplasia is treated. Note that the treatment function does not affect the number of individuals in total. The treated $\mathcal{T}T$-matrix is stored at every screening age. After treatment the population is updated and the subpopulations summed to the screened population

$$F_{screened} = \mathcal{T}T + (1 - s)p_{att}F + (1 - p_{att})F.$$

With this screening scheme implemented in the progression model we can collect the

number of infected at each time step, the number of cancers at each time step, how many CIN- and CGIN-findings there are at each screening age and we get a picture of how the cohort is distributed on the states as a function of time.

3.2 Indicators

The indicators, or the interesting numbers to study in our model computations, was the number of cancers during a lifetime, the cancer prevalence, as well as the number of findings in screening during a lifetime of a cohort. In the results of one cohort of women we monitored the lifetime number of adenocarcinomas (ADC). We also studied the neoplasia findings in screenings and summed them up from all screening rounds during the lifetime of the population cohort. We studied the lifetime number of squamous neoplasms (CIN) found in screening rounds, the lifetime number of age-specific glandular neoplasms (CGIN) found in screening rounds and the lifetime number of findings where both neoplasms were detected, (CIN,CGIN). In addition to these we studied the lifetime number of findings with a neoplasia of one type and an infection of the other type, that is $(\mathrm{CIN}, \mathrm{I}_{\mathrm{ADC}})$ and $(\mathrm{I}_{\mathrm{SCC}}, \mathrm{CGIN})$. The number of squamous cell carcinomas and adenocarcinomas can be used to mirror the reality, while studying $(\mathrm{CIN}, \mathrm{I}_{\mathrm{ADC}})$ and $(\mathrm{I}_{\mathrm{SCC}}, \mathrm{CGIN})$ has important theoretical value. The types of infections present in a neoplasia are usually not identified in clinical practice but are crucial to the possible adenocarcinoma increase. The number of $(\mathrm{CIN}, \mathrm{I}_{\mathrm{ADC}})$ that would be identified through screening would diminish the threat of adenocarcinoma, but with vaccination this is not the case anymore.

The results are presented with respect to the indicators with cohorts of 100 000 women. The results consist of prevalences of squamous cell carcinomas, adenocarcinomas, cases with both cancers present, findings in screening rounds and findings with infection of the other HPV-type. Note that the number of squamous cell carcinomas, denoted by SCC, is the sum of all squamous cell carcinomas, including the ones with adenocarcinoma and $\mathrm{HPV}_{\mathrm{ADC}}$ infections present too. The same applies to adenocarcinomas, the number of ADC include the cases co-infected with squamous cell carcinomas and $\mathrm{HPV}_{\mathrm{SCC}}$ infections.

3.3 Parameters and scenarios

In subsection 3.1.1 we presented the model states and rates between states. Table 3.2 presents the base case values for the model parameters (Table 3.1). These rates are usually assumed fixed and therefore referred to as parameters. The values in Table 3.2 are reference values, which means that if nothing else is mentioned, these values are the ones used in computations.

When deciding which parameter values to use as reference values in our model, the decision was made with two criteria in mind. One was to do the computations with common "model parameter values", used in e.g. [8]. The other was to check if these are in line with literature parameters and adjust them so that they are close to real biological values. Finding which values correspond to reality is challenging and Insinga et al. [28] reviewed literature to gather parameters used in HPV models. We used this literature review in addition to parameter estimation from [29] as a guideline for the parameters in this model.

We executed the analysis with six different populations. The populations were divided according to three different screening programs and two different levels of sexual activity (Table 3.3). The screening programs were intensive screening, standard screening and no screening, while the levels of sexual activity were categorized into average sexual activity and high sexual activity (higher than the average). These were chosen so that we can evaluate which consequences screening and vaccination have on adenocarcinomas under different conditions. The population with standard screening and average sexual activity was designed to resemble a general population in the western world and the population with intensive screening and average sexual activity to resemble the situation in Finland, where screening is more intensive due to opportunistic screening. The population with high sexual activity is a high-risk population with higher force of infection for both HPV_{SCC} and HPV_{ADC}, and was analyzed with different screening scenarios. To study the effects of vaccination, we computed the same six scenarios in Table 3.3 with vaccination as well as the difference between vaccination and no vaccination for each population.

Parameter	**Symbol**	**Value**
Natural history [1/year]		
ProgressionHPV$_{\text{SCC}}$	$\pi_{I,SCC}$	0.1
Progression HPV$_{\text{ADC}}$	$\pi_{I,ADC}$	0.1
Symptom HPV$_{\text{SCC}}$	π_{CIN}	0.02
Symptom HPV$_{\text{SCC}}$	π_{CGIN}	0.02
Clearance from I_{SCC}	$\eta_{I,SCC}$	0.6
Clearance from I_{ADC}	$\eta_{I,ADC}$	0.6
Clearance from CIN	η_{CIN}	0.1
Clearance from $CGIN$	η_{CGIN}	0.1
Force of infection		
Maximum value HPV$_{\text{SCC}}$ [1/year]	K_{SCC}	0.12
Maximum value HPV$_{\text{ADC}}$ [1/year]	K_{ADC}	0.04
Maximal age [year]	a_M	22
Tail HPV$_{\text{SCC}}$ [year]	θ_{SCC}	4
Tail HPV$_{\text{ADC}}$ [year]	θ_{ADC}	2
Screening		
Screening sensitivity HPV$_{\text{SCC}}$	s_{SCC}	0.9
Screening sensitivity HPV$_{\text{ADC}}$	s_{ADC}	0.1
Intensive screening [ages]	InS	(21, 24, 27 . . . 60)
Standard screening [ages]	StS	(30, 35, 40 . . . 60)
Attendance probability	p_{att}	0.8
Time progression		
Model enter age	a_0	10
Model exit age	a_n	70
Time step	Δt	1/52

Table 3.2: Base case parameter values.

To evaluate how the number of adenocarcinomas changed as a function of input parameter values and interventions, we performed a sensitivity analysis. We wished to know if there were certain conditions or virus type characteristics that amplified these changes in adenocarcinoma prevalence and if there are some parameters that have a greater impact than others.

To understand how screening affects the number of cancers and neoplasms the screening sensitivities s_{SCC} and s_{ADC} were analyzed. To assess how the sexual behavior alters the number of cancers and neoplasms, we analyzed the force of infection input parameters

	Sexual behavior	
	Average	Active
Intensive screening		
Standard screening		
No screening		

Table 3.3: Populations.

K_{SCC} and K_{ADC}. To understand how natural history parameters contribute we analyzed the recovery parameters $\eta_{I_{SCC}}$, $\eta_{I_{ADC}}$, η_{CIN} and η_{CGIN}. These eight parameters were chosen as a starting point for the analysis.

The sensitivity analysis was conducted by computing the lifetime number of adenocarcinomas as a function of the parameters stated above, without vaccinating the population. Then we did the same thing, but with vaccination, and compared compared the two outcomes. To determine if the two outcomes with and without vaccination differed significantly from each other, we defined a significance level. Suppose that the lifetime number of adenocarcinomas depend on a parameter value. If this lifetime number differs when comparing vaccination and no vaccination, we state that the parameter has an impact. To know which parameter value result in a difference between adenocarcinomas in a vaccinated and a non-vaccinated population, we first computed how much the maximal relative change in adenocarcinomas is without vaccination. Then we computed the same thing with vaccination and the difference between the relative changes determines if the parameter has an impact on the vaccination-induced adenocarcinoma increase. We used the relative difference instead of the absolute difference because the comparability between the parameters was clearer with the relative difference.

In addition to computing the difference in the adenocarcinoma increase, we also determined which specific parameter value resulted in the maximal relative difference. This was done with the purpose to get a theoretical limit to how much parameters can affect the number of adenocarcinomas.

To analyze how adenocarcinomas depend on a parameter, we defined the range where we perturb the parameter. Denote the number of adenocarcinomas by n, and denote a parameter by θ , and let θ vary on an interval Θ. Here Θ is an interval chosen so, that the parameter value is biologically relevant, we do not include extremely high rates that

would be impossible to have in a real life setting. Hence we do not have to take into account the question of convergence of cancer cases when θ goes to infinity.

Denote the vaccination status with v_0 for a non-vaccinated cohort and with v_1 for a vaccinated cohort. The maximal relative change of cancer cases as a function of the rate-parameter θ is given by

$$d_{v_i} = \frac{\max_{\theta\in\Theta}\{n(\theta)\} - \min_{\theta\in\Theta}\{n(\theta)\}}{\max_{\theta\in\Theta}\{n(\theta)\}}, \qquad i = 0, 1, \tag{3.13}$$

and comparing the d_{v_1} of the vaccinated cohort with the non-vaccinated d_{v_0} cohort gives and indication whether the parameter has an impact on the adenocarcinomas. In other words, if the d_{v_0} and d_{v_1} are approximately the same, the vaccine has the same effect on the number of cancers.

To know if the parameters actually have an impact on the adenocarcinoma prevalence, we defined a significance level. If the difference of adenocarcinomas as function of the parameter in a vaccinated population and a non-vaccinated population was greater than the significance level, we included the parameter into our analysis. Therefore we set that if the compared difference is above a significance level,

$$d_c = |d_{v_0} - d_{v_1}| \geq 0.025, \tag{3.14}$$

we state that the parameter has an impact. For the parameters above the significance level, we compute the parameter value with maximal impact. We define the parameter value θ_m to yield the maximal difference in adenocarcinoma cases by

$$\theta_m = \arg\max_{\theta\in\Theta}\{|n_{v1}(\theta) - n_{v0}(\theta)|\}. \tag{3.15}$$

3.4 Practical computations and model validation

The age-cohort model and the progression in time were computed by writing MATLAB scripts including the time progression with screening and vaccination schemes. Model validation of the program scripts was done by checking at each time step that the individuals in all compartments summed up to the whole population size. We also checked

that the columns of the natural history matrix summed to one at different times. For an actual example of a screening round and time progression step, see Appendix C.

Chapter 4

Results

In this chapter we illustrate the outcomes with the basic model properties. We present the prevalence distributions with and without screening and the findings from screening. We present the different populations described in Table 3.3 and their cancer prevalences without vaccination. After this the prevalences with vaccination are presented and we show how they are affected by vaccination. Lastly we introduce the parameters that we chose to variate in the sensitivity analysis, and the results from the parameter variations.

4.1 Pre-vaccination

In this section we present the results for populations without vaccination. These results are needed and used in the next section for comparison with the results from vaccinating the populations.

4.1.1 Prevalences

To illustrate what kind of distributions on the disease states the model produced, we computed prevalence distributions for an age cohort without screening and with the base case parameters in Table 3.2 before analyzing impacts of vaccination. With the base case parameters and without screening $1,1\%$ developed adenocarcinoma during their lifetime and $2,2\%$ developed squamous cell carcinoma. Most of the cancers developed between

the ages 20 and 45. The number of individuals in CIN states increase up to age 25, after which they decrease. During the lifetime of the cohort $8,2\%$ remained susceptible and $89,4\%$ recovered and acquired immunity for HPV_{SCC}, while $53,9\%$ remained susceptible and $44,7\%$ became recovered and immune to HPV_{ADC}, see Figure 4.1. The maximal prevalence for HPV_{SCC} infection was $9,9\%$ (age 21) and for HPV_{ADC} $4,7\%$ (age 24), which also is illustrated in Figure 4.1.

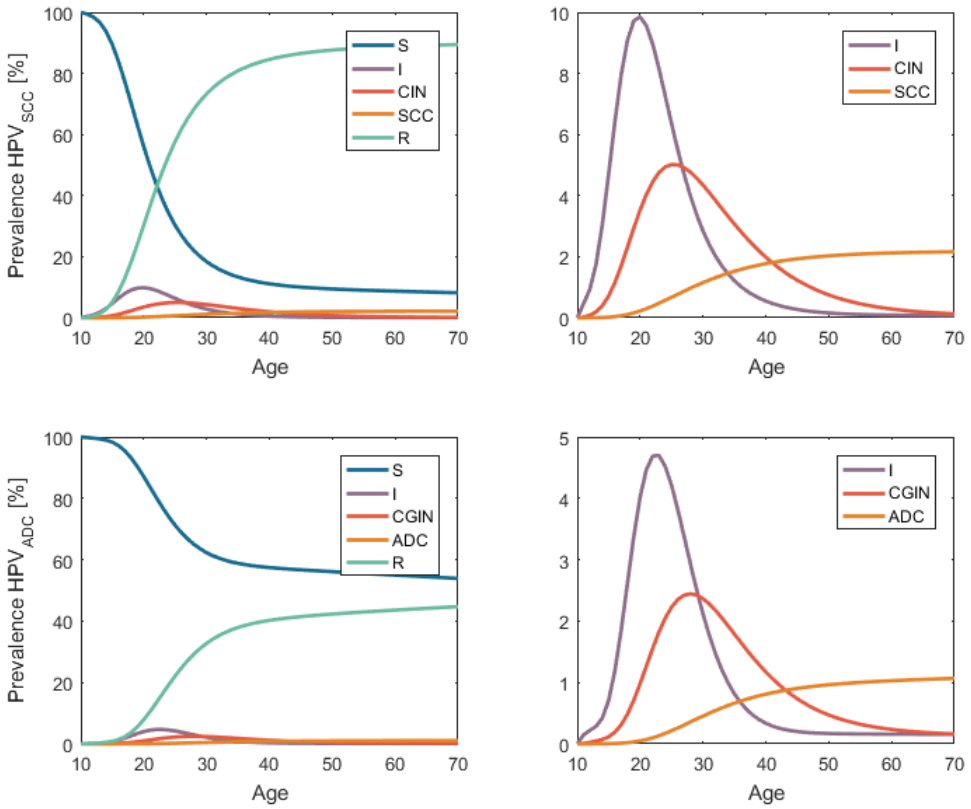

Figure 4.1: Prevalences with baseline parameters and without screening. The first row is HPV_{SCC} prevalence and the second row is HPV_{ADC} prevalence.

With base case parameters and standard screening the model resulted in $1,0\%$ developed adenocarcinomas and $1,4\%$ developed squamous cell carcinomas which is $8,3\%$ and $36,3\%$ less than without screening, respectively. While most people got infected with HPV_{SCC}, $90,3\%$ recovered, see Figure 4.2. The infection peak prevalence is $9,8\%$ for

HPV_{SCC} and declines after the age of 21. Of the population cohort only $8,2\%$ completely avoided the infection of HPV_{SCC}. The decrease in adenocarcinomas is enhanced by standard screening starting at age 30. Over half of the population remains susceptible to HPV_{ADC} during their lifetime. The infection peak prevalence for HPV_{ADC} is around age 24 at $4,7\%$. The effects of screening can be seen in Figure 4.2 as drops in CIN and CGIN numbers. The screening sensitivity is smaller for HPV_{ADC} alone, so the drops in CGIN cases at screening ages can be seen but they are not as striking as for CIN, as shown in Figure 4.2.

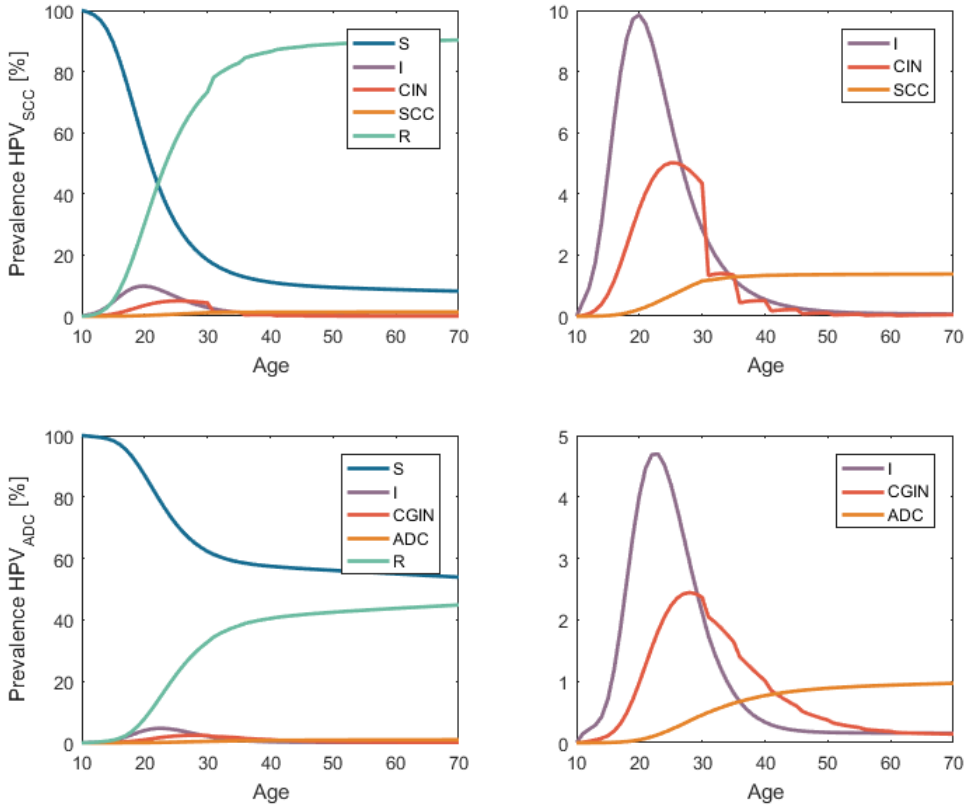

Figure 4.2: Prevalences with baseline parameters and standard screening. The first row is HPV_{SCC} prevalence and the second row is HPV_{ADC} prevalence.

4.1.2 Screening findings

Screening was conducted with two different screening programs. Standard screening means that the cohort is screened every fifth year between age 30 and 60, while intensive screening means that the cohort is screened every third year between 21 and 60. We also computed results without screening.

In screening the number of precancerous cases, CIN and CGIN-cases, were collected and the number of findings in screening varied with the screening intervals. Consider a cohort of 100 000 women. With standard screening the number of CIN findings were over 3129 at the first screening round at age 30, while the second screening at age 35 produced 974 CIN findings and the number of findings decreased from that age at each screening (Figure 4.3). The lifetime number of CIN findings from all screening rounds was 4783. The number of CGIN findings were also highest at age 30 with 256 findings and decreased at each screening round after the first. The lifetime number of CGIN findings from all screening rounds was 600. The number of cancers were not detected in screening, because of the model assumption that if a precancerous lesion progressed to cancer, the cancers would be found by their symptoms and not by the screening program.

The findings, which are crucial to the detection and treatment of adenocarcinoma, are the ones with both CIN and CGIN states present. With standard screening the first screening round at age 30 revealed 75 precancerous findings with both CIN and CGIN present after which the co-findings rapidly declined. The lifetime number of findings in a cohort of 100 000 women with both types present from all screening rounds was 97 with standard screening.

With standard screening the number of findings with CIN and I_{ADC} present was 66 at the first screening at age 30, 8 at age 35 and 1 at age 40. The detailed figures from these can be found in Appendix A in tables A.3 and A.4.

The number of lifetime squamous cell carcinomas with standard screening was 1379, while the number of lifetime adenocarcinomas was 968.

With intensive screening of the cohort of 100 000 women the number of CIN findings were 2907 at age 21, and decreased with every screening round after that. The lifetime number of CIN findings was 8953. The number of CGIN findings was not decreasing from the first screening round, but was at its highest at age 27 with 206 findings, (Figure 4.3),

where after the number of findings in each screening round declines. The lifetime number of CGIN findings with intensive screening was 1247. The findings with both CIN and CGIN present declined after age 23 with 42 findings, and the lifetime number of findings with both types present was 154.

Even though the number of findings at the first screening round was higher with standard screening compared to intensive, the total number of findings is higher with intensive screening. This means that the more we screen, the more we find. Recall that in this model the cancers in the late stages (SCC and ADC) are not found in screening, but are found by theirs symptoms outside the screening program. Therefore the cancer findings are not reported at screenings, but in the next section.

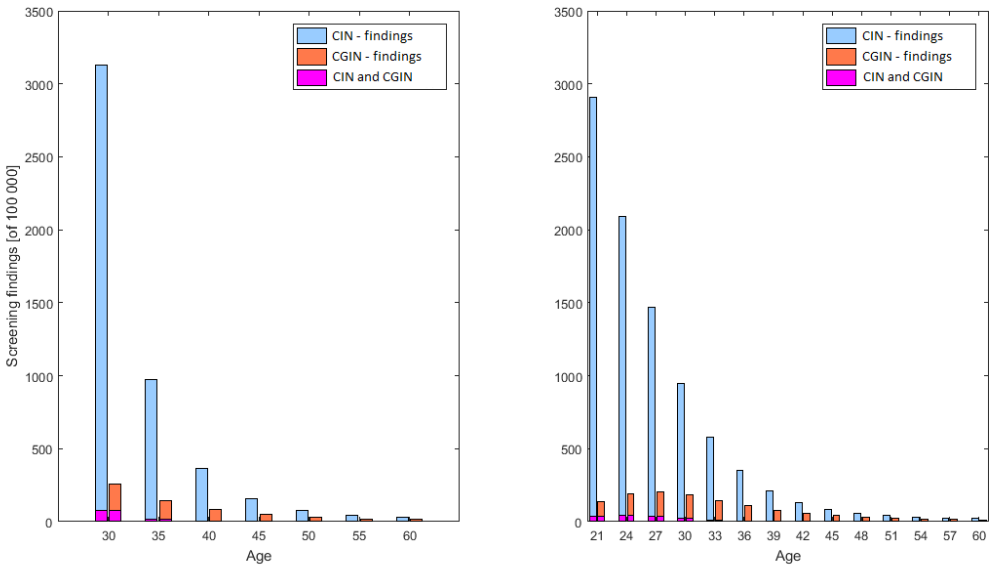

Figure 4.3: Number of CIN-findings and CGIN-findings at each screening age. Left: Standard screening. Right: Intensive screening.

4.1.3 Baselines for different screening scenarios

We computed the model outcomes with cohorts from different populations without vaccination, to know what to compare with when vaccinating. The populations were the average sexual activity level population with intensive, standard and no screening and the high sexual activity population with intensive, standard and no screening, as presented in section 3.3. The cohort size is 100 000 throughout the chapter.

In the population with high sexual activity the number of adenocarcinomas were the highest. In a birth cohort in this group of 100 000 women, no screening led to 2155 adenocarcinomas during their lifetime (Table 4.2). Standard screening in the population with high sexual activity a led to 1994 adenocarcinomas, while intensive screening led to 1722 adenocarcinoma cases during the lifetime. The number of squamous cell carcinomas was also high without screening with 2376 cases. Standard and intensive screening led to 1882 and 1000 cases of squamous cell carcinoma respectively.

Average sexual activity resulted in less adenocarcinomas and squamous cell carcinomas compared to the population with high sexual activity (Table 4.1). In a cohort of 100 000 women the number of adenocarcinomas was 1067 without screening, 968 with standard screening and 857 with intensive screening. The respective numbers for squamous cell carcinomas was 2162 without screening, 1379 with standard screening and 683 with intensive screening.

No screening resulted, naturally, in no precancerous findings. Intensive screening compared to standard screening led to more findings of both CIN and CGIN for both the high and average sexual activity levels (Table 4.2 and Table 4.2).

	Sexual activity: average							
	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Intensive screening	683	857	6	8953	1247	154	305	39
Standard screening	1379	968	14	4784	600	97	76	8
No screening	2162	1067	23	0	0	0	0	0

Table 4.1: Average sexual activity, different screenings. The SCC and ADC are numbers of squamous cell carcinomas and adenocarcinomas in a lifetime, CIN and CGIN are neoplasia findings, and I_{SCC} and I_{ADC} are infected but not neoplastic states discovered with neoplastic findings. Cohort size: 100 000.

	Sexual activity: high							
	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Intensive screening	1000	1722	18	8281	2515	372	863	41
Standard screening	1882	1994	38	2991	984	132	62	1
No screening	2376	2155	51	0	0	0	0	0

Table 4.2: Sexually active population, different screenings. The SCC and ADC are numbers of squamous cell carcinomas and adenocarcinomas in a lifetime, CIN and CGIN are neoplasia findings, and I_{SCC} and I_{ADC} are infected but not neoplastic states discovered with neoplastic findings. Cohort size: 100 000.

4.2 Post-vaccination

In this section we present the results for vaccinated populations. We computed the results with the same inputs for the same populations as in the previous chapter but with vaccination of the cohort. Thus we could compare the results of identical populations where vaccination was the only difference. The vaccine offers full protection against infections of HPV_{SCC} and no protection against HPV_{ADC}. The results in this section are presented in cohorts with 100 000 women.

For the cohort with average sexual activity the number of adenocarcinomas increased with vaccination with both intensive and standard screening (Table 4.3). The increase in adenocarcinomas was positive with 25 cases $(2,9\%)$ with intensive screening comparing vaccination with no vaccination. With intensive screening the number of precancerous CGIN findings decreased by 108 cases (8,7 %) with vaccination and the number of co-infected CIN- and I_{ADC}-findings decreased with 305 cases (100 %) with vaccination. The number of squamous cell carcinomas decreased from 683 to 0 (100 %) with vaccination and the number of CIN-findings decreased from 8953 to 0 (100 %), as all the precancerous lesions and cancers associated with HPV_{SCC} are eliminated as a result of vaccination.

Standard screening of the cohort with average sexual activity the vaccination increased the number of adenocarcinomas with 15 cases (1,5 %) (Table 4.3), wich is still a positive increase but less than with intensive screening. The total number of adenocarcinomas (983 with vaccination) is, however, higher than with intensive screening (882 with vaccination). The precancerous CGIN-findings decreased by 78 cases (13,0 %). The co-infected CIN- and I_{ADC}-findings decreased with 76 (100 %). There was also a anticipated decrease of

1379 (100 %) squamous cell carcinoma cancers and a decrease of 4784 CIN-findings (100 %) with standard screening.

To compare the previous results to the situation without screening, we found that no screening of an average sexual activity level population led to 1067 cases of adenocarcinoma with and without vaccination (Table 4.3), there was no increase in adenocarcinoma since there was no screening and the vaccination alone does not result in a change in adenocarcinoma. The vaccination eliminated the squamous cell carcinoma entirely, from 2162 to 0 (100 %). No screening led naturally to no findings.

If we would not only start vaccinating a population with average sexual activity, but also decrease the screening frequencies from intensive to standard screening the increase of adenocarcinomas would be 126 cases (14,7 %) which is significantly higher than with only vaccination. If we would decrease screening from intensive to no screening and start vaccinating, the adenocarcinoma increase would be even greater with 210 cases (24,5 %) more. Both the vaccination and the screening frequency affected these numbers, the increase is not only a result of vaccination.

Vaccination had an impact on the adenocarcinoma increase in the population with high sexual activity. For the population with high sexual activity level and intensive screening the number of adenocarcinomas increased with 63 cases (3,7 %) with vaccination (Table 4.4) which is a greater increase compared to the average sexual activity level. Vaccination of the population with intensive screening led to an decrease of 258 (10,3 %) precancerous CGIN-findings. The co-infected CIN and I_{ADC}-findings decreased from 863 to 0 (100 %) with vaccination. Vaccination led also to a decrease of 1000 squamous cell carcinomas (100 %) and a decrease of 8281 CIN findings (100 %).

Standard screening and vaccination of a population with high sexual activity led to an adenocarcinoma increase of 19 cases (1,0 %), less than with intensive screening. We observed a decrease of 107 (10,8 %) precancerous CGIN-findings (Table 4.4), a relative decrease quite close to the one with intensive screening. A decrease of 62 cases (100 %) for the co-infected CIN and I_{ADC}-findings was also observed with vaccination. With full vaccine coverage the squamous cell carcinomas were completely eliminated (from 1882 to 0, 100 % decrease) and the same applied naturally for the CIN findings.

With no screening the vaccination had no impact on the number of adenocarcinomas

of the population with high sexual activity (Table 4.4). Without screening there are no effects of vaccination against HPV_{SCC} on adenocarcinoma. The squamous cell carcinomas dropped from 2376 to 0 (100 %) and there were no CIN or CGIN findings without screening.

If vaccination would be combined with a decrease in screening frequencies, the adenocarcinoma increase would be more prominent. We studied a cohort with high sexual activity, vaccination and intensive screening and compared this to screening the cohort with standard screening. We got an adenocarcinoma increase of 291 cases (16,9 %) and switching to no screening would give a total increase of 433 (25,1 %) new adenocarcinomas compared to the situation without vaccination and with intensive screening.

When comparing the number of adenocarcinomas with and without vaccination (Table 4.3 and Table 4.4) we see that the sexual activity and the screening frequency both have an impact on the number of cancers. The sexually active population with intensive and standard screening develops 3,7 % and 1,0 % more adenocarcinomas, respectively, when vaccinating, while the population with average sexual activity and intensive and standard screening develops 2,9 % and 1,4 %, respectively, more adenocarcinomas with vaccination.

4.3 Sensitivity analysis

4.3.1 Choosing parameters to variate

To understand which parameters have an impact on adenocarcinomas, we followed the procedure described by Equations 3.13, 3.14 and 3.15. We computed the d_c-values with standard and intensive screening, and we observed that the screening affected the d_c-value. All d_c-values were higher with intensive screening compared to standard screening, which means that the difference in adenocarcinomas between vaccinating and not vaccinating is greater with intensive screening. Parameters relating to HPV_{ADC} had d_c-values below 0,025 and were excluded from the significant parameters. Computing with Equation 3.14, the results with $d_c \geq 0,025$ are presented in Table 4.5. As long as one of the d_c-values was above the significance level, the parameter was considered meaningful.

Sexual activity: average								
	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Intensive screening	683	857	6	8953	1247	154	305	39
Intensive screening and vaccination	0	882	0	0	1139	0	0	0
Difference	-683	25	-6	-8953	-108	-154	-305	-39
Rel. difference (%)	-100,0 %	2,9 %	-100,0 %	-100,0 %	-8,7 %	-100,0 %	-100,0 %	-100,0 %
Standard screening	1379	968	14	4784	600	97	76	8
Standard screening and vaccination	0	983	0	0	522	0	0	0
Difference	-1379	15	-14	-4784	-78	-97	-76	-8
Rel. difference (%)	-100,0 %	1,5 %	-100,0 %	-100,0 %	-13,0 %	-100,0 %	-100,0 %	-100,0 %
No screening	2162	1067	23	0	0	0	0	0
No screening and vaccination	0	1067	0	0	0	0	0	0
Difference	-2162	0	-23	0	0	0	0	0
Rel. difference (%)	-100,0 %	0,0 %	-100,0 %	-	-	-	-	-

Table 4.3: Population with average sexual activity with different screening intervals, without and with vaccination and the difference between the two. Cohort size: 100 000.

Sexual activity: active								
	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Intensive screening	1000	1722	18	8281	2515	372	863	41
Intensive screening and vaccination	0	1785	0	0	2257	0	0	0
Difference	1000	63	-18	-8281	-258	-372	-863	-41
Rel. difference (%)	-100,0 %	3,7 %	-100,0 %	-100,0 %	-10,3 %	-100,0 %	-100,0 %	-100,0 %
Standard screening	1882	1994	38	2991	984	132	62	1
Standard screening and vaccination	0	2013	0	0	877	0	0	0
Difference	-1882	19	-38	-2991	-107	-132	-62	-1
Rel. difference (%)	-100,0 %	1,0 %	-100,0 %	-100,0 %	-10,8%	-100,0 %	-100,0 %	-100,0 %
No screening	2376	2155	51	0	0	0	0	0
No screening and vaccination	0	2155	0	0	0	0	0	0
Difference	-2376	0	-51	0	0	0	0	0
Rel. difference (%)	-100,0 %	0,0 %	-100,0 %	-	-	-	-	-

Table 4.4: Population high sexual activity with different screening intervals and without and with vaccination and the difference between the two. Cohort size: 100 000.

		d_c	
Parameter	**Symbol**	**Standard screening**	**Intensive screening**
Screening sensitivity HPV_{SCC}	s_{SCC}	0.5%	3.08%
Clearance from I_{ADC}	$\eta_{I,ADC}$	1.25%	6.37%
Clearance from CIN	η_{CIN}	1.86%	4.88%
Maximum value HPV_{ADC}	K_{ADC}	0.4%	2.93%

Table 4.5: Assessment of parameters, where d_c-values are computed with equation 3.14

4.3.2 Parameter variation

To analyze the impact that the parameters, chosen above, had on the adenocarcinoma prevalence, the adenocarcinomas were plotted as functions of the parameter values. This was done by keeping all other parameters according to Table 3.2 and varying one parameter in a suitable interval. The results are presented in figure Figure 4.4 and Figure 4.5 where the cohorts are with and without vaccination. The cancer cases on the vertical axis are all adenocarcinoma cases, because it is in these we expect to observe type replacement. The same plots for squamous cell carcinomas are found in Appendix A.

The plots on the right hand side in figure Figure 4.4 and Figure 4.5 show little difference between vaccinated and non-vaccinated cohorts. That is because the HPV_{ADC} parameters relate directly to the HPV_{ADC} cancers. The reason why the lines do not coincide completely, is because ADC also contains the co-cancer (SCC,ADC) and without vaccination some HPV_{ADC} infections are treated with the CIN findings. This was checked through doing the same computations but without screening, in which case the number of cancers coincided between the vaccinated and non-vaccinated cohorts.

The screening sensitivity parameter for squamous cell carcinomas affected the number of adenocarcinomas. In the upper left plot of Figure 4.4 the lifetime number of adenocarcinomas decrease with increased screening sensitivity for HPV_{SCC}, while for a vaccinated cohort the number of cancer cases remains constant. This implies that a better the sensitivity for screening squamous cell carcinomas leads to less cases of adenocarcinoma since the screening detects some of the CGIN:s too. The difference in adenocarcinoma prevalence in vaccinated and not vaccinated populations is largest when the screening

for HPV_{SCC} has a perfect sensitivity, $s_{SCC} = 1$. With this perfect screening sensitivity the impact is maximal and the adenocarcinomas increase with 15,8 cases $(1,6\%)$ when vaccinating the standard population and with 26,1 cases $(3,1\%)$ when vaccinating the intensive-screening population, see Table 4.6.

Varying the maximum of the force of infection parameter K_{SCC} also had an impact on the adenocarcinoma prevalence. The lifetime number of adenocarcinomas as a function of the force of infection maximum K_{SCC} shows an interesting property in Figure 4.4, where the adenocarcinoma lifetime incidence is first decreasing and then increasing as a function of K_{SCC}. There are two main reasons for this behavior, firstly the number of ADC including the co-cancers (SCC,ADC) results in the non-monotonous behavior, since the number of SCC, and hence also (SCC,ADC), increase as a function of K_{SCC}. When K_{SCC} and K_{ADC} coincide, the flows into the CIN and CGIN states are approximately alike, and a large fraction of these are treated because of finding a CIN. When the force of infection maximum for HPV_{SCC} is higher compared to HPV_{ADC}, the flow to CIN is greater than to CGIN and when treatment is started because of screenings the part in CGIN but not yet in CIN is treated and found, which allows them to still develop adenocarcinoma but the chance of finding these in screening are small. This property is related to the age-dependency of the force of infection intertwined with screening also being age-determined. The maximal difference in adenocarcinomas between a vaccinated and non-vaccinated cohort is when $K_{SCC} = 0.1$. This limit value led to an increase of 14,3 cases $(1,5\%)$ with standard screening and 23,9 cases $(2,8\%)$ with intensive screening. Hence the impact of the force of infection maximum is less than the impact of the screening sensitivity, see Table 4.7.

The clearance rates $\eta_{I,SCC}$ and η_{CIN} had the largest effect on the adenocarcinoma prevalence. The difference in adenocarcinoma prevalence between a fully vaccinated population and a non-vaccinated population is largest when the clearance rates are at zero, as seen in Figure 4.5. The limit value that led to the greatest increase in adenocarcinomas was $\eta_{I,SCC} = 0$. Standard screening and $\eta_{I,SCC} = 0$ led to an increase of 105,7 cases $(12,0\%)$ in adenocarcinoma prevalence, while intensive screening led to an increase of 147,4 cases $(20,1\%)$, see Table 4.8. Clearance from CIN-state had also an impact, $\eta_{CIN} = 0$ and standard screening increased the adenocarcinoma prevalence with 32,7

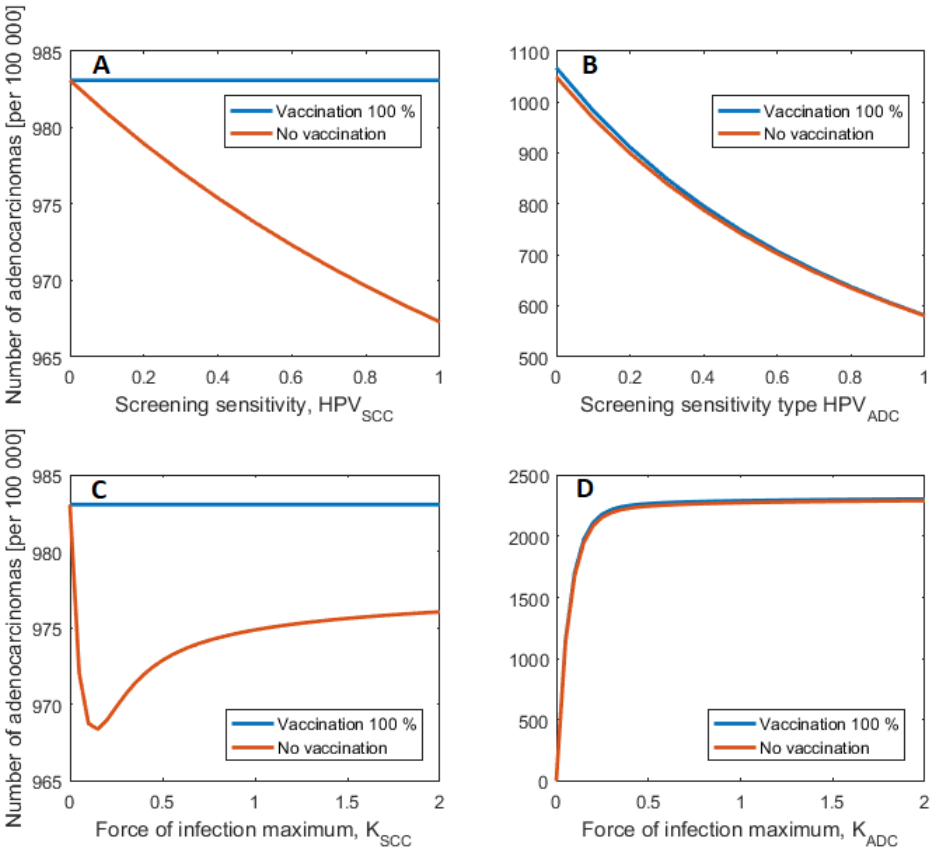

Figure 4.4: The lifetime number of adenocarcinomas per 100 000 women with standard screening and varying value for **(A)** screening sensitivity s_{SCC}, **(B)** screening sensitivity s_{ADC}, **(C)** force of infection maximum K_{SCC} and **(D)** force of infection maximum K_{ADC}.

cases $(3,4\%)$ while intensive screening led to an increase of 34,2 cases $(4,0\%)$.

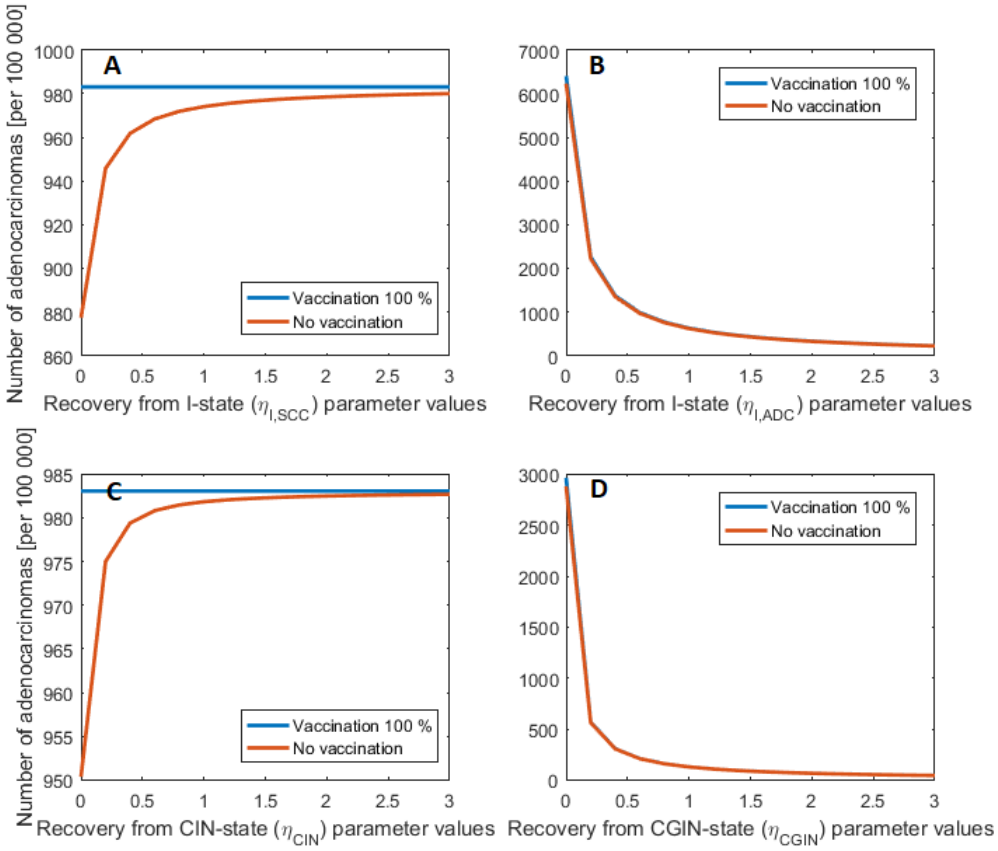

Figure 4.5: The lifetime number of adenocarcinomas per 100 000 women with standard screening and varying value for **(A)** recovery rate $\eta_{I,SCC}$, **(B)** recovery rate $\eta_{I,ADC}$, **(C)** recovery rate η_{CIN} and **(D)** recovery rate η_{CGIN}.

	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Standard screening	1333,7	967,3	13,1	5054,4	606,2	103,4	83,0	7,7
Standard screening with vaccination	0,0	983,1	0,0	0,0	522,4	0,0	0,0	0,0
change	-1333,7	15,8	-13,1	-5054,4	-83,8	-103,4	-83,0	-7,7
change (%)	-100,0 %	1,6 %	-100,0 %	-100,0 %	-13,8 %	-100,0 %	-100,0 %	-100,0 %
Intensive screening	625,0	855,6	5,5	9303,2	1250,1	156,8	321,9	39,1
Intensive screening with vaccination	0,0	881,7	0,0	0,0	1138,9	0,0	0,0	0,0
change	-625,0	26,1	-5,5	-9303,2	-111,3	-156,8	-321,9	-39,1
change (%)	-100,0 %	3,1 %	-100,0 %	-100,0 %	-8,9 %	-100,0 %	-100,0 %	-100,0 %

Table 4.6: Results for standard and intensive screening with $s_{SCC} = 1$.

	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Standard screening	1276,7	968,8	12,6	4774,5	598,6	95,0	73,5	8,5
Standard screening with vaccination	0,0	983,1	0,0	0,0	522,4	0,0	0,0	0,0
change	-1276,7	14,3	-12,6	-4774,5	-76,2	-95,0	-73,5	-8,5
change (%)	-100,0 %	1,5 %	-100,0 %	-100,0 %	-12,7 %	-100,0 %	-100,0 %	-100,0 %
Intensive screening	637,8	857,8	5,7	8605,2	1242,6	147,2	281,7	39,0
Intensive screening with vaccination	0,0	881,7	0,0	0,0	1138,9	0,0	0,0	0,0
change	-637,8	23,9	-5,7	-8605,2	-103,7	-147,2	-281,7	-39,0
change (%)	-100,0 %	2,8 %	-100,0 %	-100,0 %	-8,3 %	-100,0 %	-100,0 %	-100,0 %

Table 4.7: Results for standard and intensive screening with $K_{SCC} = 0, 1$.

	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Standard screening	7323,0	877,4	72,3	45061,2	1094,7	711,5	493,3	116,2
Standard screening with vaccination	0,0	983,1	0,0	0,0	522,4	0,0	0,0	0,0
change	-7323,0	105,7	-72,3	-45061,2	-572,3	-711,5	-493,3	-116,2
change (%)	-100,0 %	12,0 %	-100,0 %	-100,0 %	-52,3 %	-100,0 %	-100,0 %	-100,0 %
Intensive screening	4092,3	734,2	36,4	64305,8	1833,9	966,6	1374,0	316,3
Intensive screening with vaccination	0,0	881,7	0,0	0,0	1138,9	0,0	0,0	0,0
change	-4092,3	147,4	-36,4	-64305,8	-695,1	-966,6	-1374,0	-316,3
change (%)	-100,0 %	20,1 %	-100,0 %	-100,0 %	-37,9 %	-100,0 %	-100,0 %	-100,0 %

Table 4.8: Results for standard and intensive screening with $\eta_{I,SCC} = 0$.

	SCC	ADC	(SCC, ADC)	CIN	$CGIN$	$(CIN, CGIN)$	(CIN, I_{ADC})	$(I_{SCC}, CGIN)$
Standard screening	2320,7	950,4	22,9	10695,5	696,5	217,0	167,4	7,7
Standard screening with vaccination	0,0	983,1	0,0	0,0	522,4	0,0	0,0	0,0
change	-2320,7	32,7	-22,9	-10695,5	-174,0	-217,0	-167,4	-7,7
change (%)	-100,0 %	3,4 %	-100,0 %	-100,0 %	-25,0 %	-100,0 %	-100,0 %	-100,0 %
Intensive screening	880,9	847,5	7,8	12139,2	1285,6	208,7	412,1	39,1
Intensive screening with vaccination	0,0	881,7	0,0	0,0	1138,9	0,0	0,0	0,0
change	-880,9	34,2	-7,8	-12139,2	-146,8	-208,7	-412,1	-39,1
change (%)	-100,0 %	4,0 %	-100,0 %	-100,0 %	-11,4 %	-100,0 %	-100,0 %	-100,0 %

Table 4.9: Results for standard and intensive screening with $\eta_{CIN} = 0$.

Chapter 5

Discussion

The purpose of this study was to determine if vaccinating a population in a screening program increases the number of adenocarcinomas with a vaccine that only protects against viruses that are found in squamous cell carcinoma. We modeled the mechanism with a deterministic two-type HPV model. We developed a computational model with screening and vaccination, and computed results for six different cohorts of women. We found that the vaccination-induced increase in adenocarcinoma prevalence was positive but small and that sexual activity and screening intervals had an impact on the adenocarcinoma increase.

Our results indicate that there is an increase in adenocarcinomas in all the model-populations. This increase is however minor compared to the decrease in squamous cell carcinomas due to vaccination, and the combined number of cancers is smaller due to vaccination in all populations. Based on our results the increase in adenocarcinomas is dependent of the screening frequency. In a population with intensive screening and vaccination, the relative increase in adenocarcinomas was higher than in a population with standard screening and vaccination. We observed that when there was an increase in adenocarcinomas as a result of vaccination, there was also a reduction in CGIN findings. This implies that there is a relationship between the number of CGIN findings and the adenocarcinoma prevalence. With total vaccination coverage the CIN-findings were reduced to zero and therefore also the findings with co-infections of CIN and CGIN as well as CIN and I_{ADC} were reduced to zero, so that these were not found in screening. Our

results showed that if there was an increase in adenocarcinoma, there was also a reduction in precancerous CGIN findings and combined CIN- and I_{ADC}-findings. This implies that there is a relationship between the increase in adenocarcinomas and the number of HPV_{ADC} infections that are not found in screening when vaccinating. Based on our results, the vaccination-induced adenocarcinoma increase was greatest when vaccination was combined with a reduction of screening frequency.

In the screening findings that the model produced, we observed that the number of co-infections, where both strains had proceeded to precancerous stages, was higher with intensive screening compared to standard screening. Since the combined CIN- and HPV_{ADC}-infections are a crucial aspect, fewer co-infections detected in screenings could lead to a higher number of adenocarcinomas in a screened and vaccinated population. In the model with the base case parameters most infections had already progressed to cancer before the start of screening when we studied standard screening. Therefore the intensive screening might present a more realistic outcome.

There are additional circumstances that enhance and affect the adenocarcinoma increase. A low recovery rate for the states precessing squamous cell carcinoma had the greatest impacts on the adenocarcinoma increase. The chance that the recovery rate for HPV 16 would be zero is very small, both for infection and CIN. The probability that an infection clears by itself is high, around 80% of infections clear spontaneously. Hence the increase of adenocarcinomas with zero recovery from precancerous squamous cell carcinoma can be considered to have mainly theoretical value. The sensitivity of screening tests is high [30] so the impact of vaccination and screening increasing the number of adenocarcinomas is possible and probable and one could expect an increase as predicted in the results. The force of infection relates to the type of population or cohort that we model, and in a population with higher sexual activity, the adenocarcinoma increase is somewhat more prominent compared to an average population when both are participating in intensive screening.

Taking our results into consideration, a possibility of adenocarcinoma increase as a result of screening and vaccination should be taken into account when assessing vaccination and screening programs. The results imply that the number of cancers prevented by vaccines is at least fourfold and in most cases over tenfold the number of adenocarcino-

mas caused indirectly. Therefore the increase in adenocarcinomas does not pose a strong argument against vaccinations.

As with most modeling studies, simplifying parameter choices and model choices were made for the sake of clarity and computability and may be a limiting factor. The force of infection could be modeled more accurately with a contact model to get a more reality-like situation, but this was disregarded on purpose because of the focus on the development of cancers instead of the transmission dynamics. Some of the base case parameters can be unrealistic in a real life setting, despite our attempts to adjust them to parameters established in literature. This is certainly true since different communities have different structures, which affect the parameters as well. Our model-HPV-types are also not completely identical to HPV 16 and 45. In reality HPV 16 causes some adenocarcinoma and HPV 45 some squamous cell carcinoma, so the numbers in the results are not equivalent to HPV 16 and 45, but form a guideline. Screening aside, the virus types were assumed independent of each other, which is a plausible assumption [15]. The natural history parameters were assumed independent of age, which is an assumption supported by literature [29].

Considering population-level dynamics instead of individual-level dynamics is common when modeling biology with mathematics. A deterministic model is a good choice for accurate and fast computations for one or a few virus types and large populations, but becomes rapidly too complex with many virus strains. A stochastic model on the other hand is efficient when dealing with many strains, or with few individuals. We chose a deterministic model, since the number of disease states was manageable for a deterministic one. For the sake of clarity and computability our model is a simplification of a real life scenario.

The results in this thesis should be assessed as an indicator of what could happen in a real life situation. Reality is of course far more complex than what is described in the model we developed, but in this study we found limiting bounds for how much adenocarcinomas could increase, which means that in real life the situation should not be worse than these results imply.

Further analysis could be conducted by focusing on adjusting the parameters even more close to the reality. This could give an even more realistic prediction of the adeno-

carcinoma prevalence in women. That being said, the new nonavalent vaccine protects against all the virus types in this study and therefore future generations vaccinated with the nonavalent vaccine do not have to be concerned with the screening- and vaccination-induced adenocarcinoma increase. In addition to this, the bivalent vaccine provides cross protection against HPV 45, which is highly represented in adenocarcinomas whereas the quadrivalent vaccine, modeled in this thesis, does not protect against HPV 45 to the same extent.

Even though the quadrivalent vaccine has been in use for a decade the mechanisms of adenocarcinoma increase have remained unclear. This study proposes insight in what to expect in the following years of screening. Based on our results, vaccinating a screened population increased the adenocarcinoma prevalence in all our proposed types of populations, although the increase was minor.

In conclusion we predict a small increase for adenocarcinomas associated with the HPV types which the vaccine does not protect against. An increase in adenocarcinomas due to the effects of screening combined with vaccination is likely. How clearly this minor increase will be observed is would be the topic of another study, but it can be an important aspect to bear in mind that a woman vaccinated against HPV can be developing an adenocarcinoma tumor. Our study has shown the importance of taking into account the risk of adenocarcinomas in women vaccinated against HPV.

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Appendices

Appendix A

Additional tables

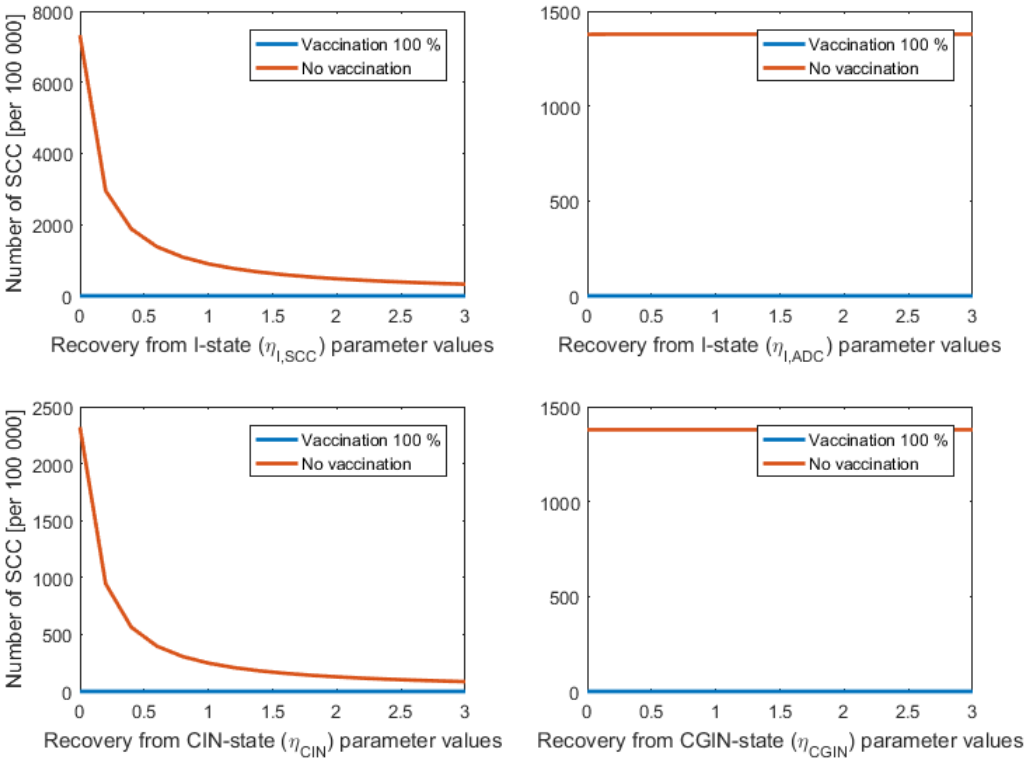

Figure A.1: The lifetime number of squamous cell carcinomas per 100 000 women with standard screening. **First row:** The number of squamous cell carcinomas during a lifetime as a function of recovery rate from infection. **Second row:** The number of squamous cell carcinomas during a lifetime as a function of the recovery rate from the precancerous state.

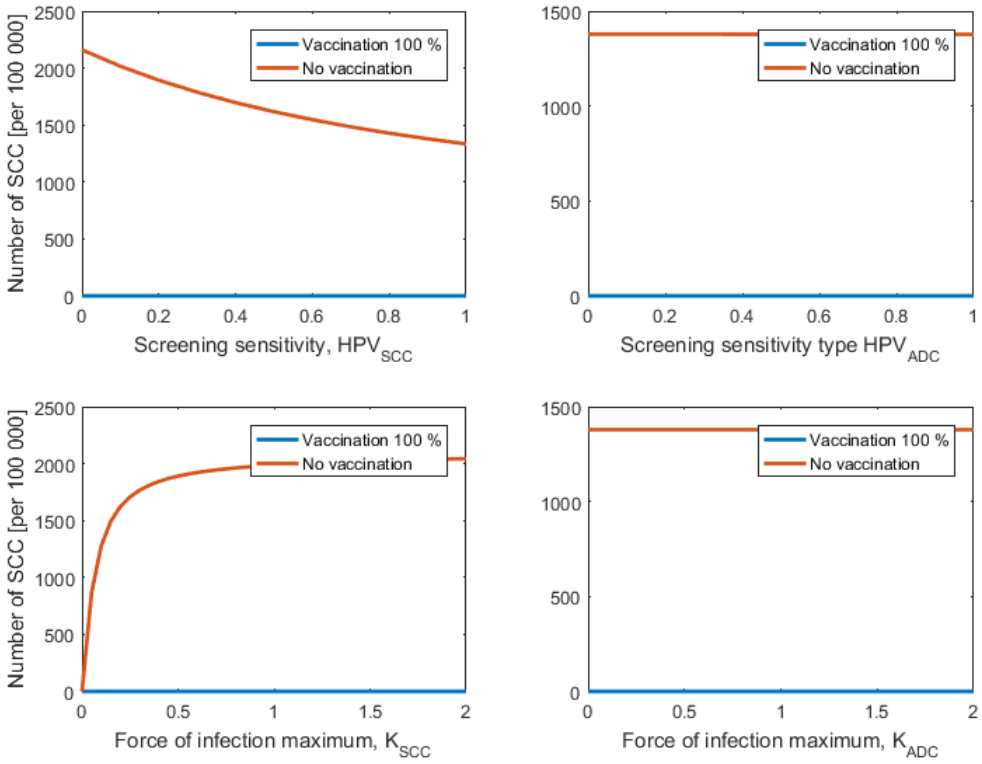

Figure A.2: The lifetime number of squamous cell carcinomas per 100 000 women with standard screening. **First row:** The number of squamous cell carcinomas during a lifetime as a function of screening sensitivity. **Second row:** The number of squamous cell carcinomas during a lifetime as a function of the force of infection maximum K. Screening: standard, cohort size: 100 000.

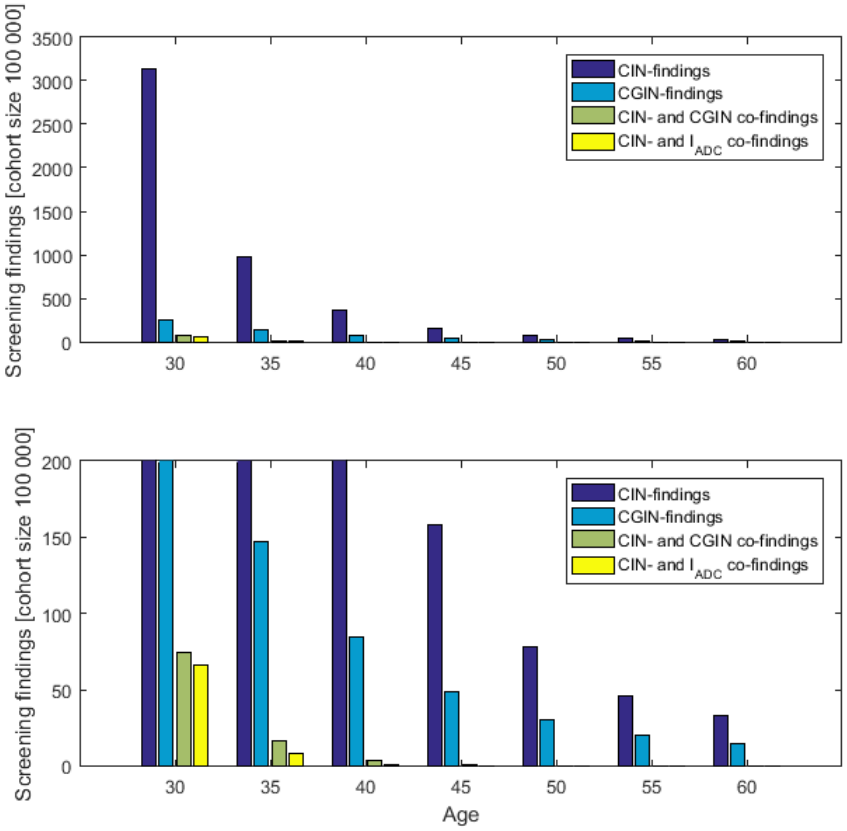

Figure A.3: Findings from standard screening. Cohort size: 100 000.

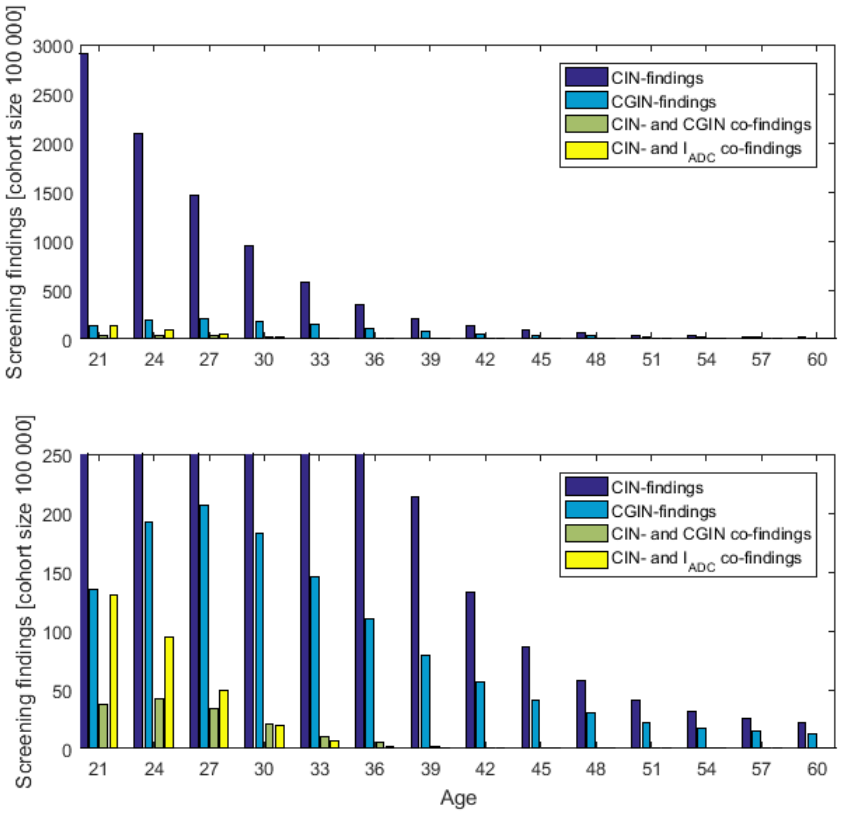

Figure A.4: Findings from intensive screening. Cohort size: 100 000.

Appendix B

Markov chains

Markov processes are powerful tools in modelling random processes in time. The idea is simple, any future state of a random process is determined only by the current state and is unaffected by the past. A process like this is called a *Markov process*. If the process can attain only a finite number of states, it is called a *Markov chain*. The formal definitions are presented below.

Let I be a countable set, and let the elements i in the state space I be states. Now $\lambda = (\lambda_i : i \in I)$ is a measure of I if the measure is finite $0 \leq \lambda_i \leq \infty$ for all $i \in I$.

Definition B.1. The measure λ is a distribution if

$$\sum_{i \in I} \lambda_i = 1.$$

Recall that a random variable X taking values in I is a function $X : \Omega \to I$ in a probability space $(\Omega, \mathcal{F}, \mathbb{P})$, and λ defines a distribution when we let

$$\lambda_i = \mathbb{P}(X = i) = \mathbb{P}(\{\omega : X(\omega) = i\}).$$

A matrix is called a *stochastic matrix*, or a *transition probability matrix* if every column sums to 1. We define $\mathbf{P}$ to be a stochastic matrix, in which all entries are non-negative and the entry p_{ij} is the probability of transitioning from state j to state i. Using this matrix we can define Markov chain.

Definition B.2. $(X_n)_{n\geq 0}$ is a Markov chain with initial distribution λ and a transition matrix P if

(i) X_0 has the distribution λ,

(ii) X_n has distribution $(p_{ij} : j \in I)$ and is independent of $X_{n-1}, X_{n-1}, \ldots, X_0$. In other words, $\mathbb{P}(X_{n+1} = i_{n+1}|X_0 = i_1, \ldots, X_n = i_n) = \mathbb{P}(X_{n+1} = i_{n+1}|X_n = i_n) = \lambda p_{i_n i_{n+1}}$

Appendix C

Model demonstration and validation: a screening round and time progression step

We performed one screening round with a time progression step, in order to demonstrate the mechanisms behind the simulations. This computation serves also as a model validation, as we checked that the program gives the same result as this computation done by hand.

Recall that the distribution between the two types of HPV states is in matrix form

$$F(t) = \begin{bmatrix} f_{S,S} & f_{S,I} & f_{S,CGIN} & f_{S,ADC} & f_{S,R} & f_{S,V} \\ f_{I,S} & f_{I,I} & f_{I,CGIN} & f_{I,ADC} & f_{I,R} & f_{I,V} \\ f_{CIN,S} & f_{CIN,I} & f_{CIN,CGIN} & f_{CIN,ADC} & f_{CIN,R} & f_{CIN,V} \\ f_{SCC,S} & f_{SCC,I} & f_{SCC,CGIN} & f_{SCC,ADC} & f_{SCC,R} & f_{SCC,V} \\ f_{R,S} & f_{R,I} & f_{R,CGIN} & f_{R,ADC} & f_{R,R} & f_{R,V} \\ f_{V,S} & f_{V,I} & f_{V,CGIN} & f_{V,ADC} & f_{V,R} & f_{V,V} \end{bmatrix}$$

and suppose that $t = 30$. Assume that the specific distribution at this age is

$$F(30) = \begin{bmatrix} 0.20 & 0.01 & 0.01 & 0.01 & 0.10 & 0 \\ 0.01 & 0.05 & 0.01 & 0.01 & 0.05 & 0 \\ 0.01 & 0.01 & 0.01 & 0.01 & 0.05 & 0 \\ 0.01 & 0.01 & 0.01 & 0.01 & 0.01 & 0 \\ 0.15 & 0.01 & 0.05 & 0.01 & 0.18 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The sensitivity to detect a CIN state is $s_{SCC}(CIN) = 0.9$ for the type alone, $s_{ADC}(CGIN) = 0.1$ for type alone and therefore $s(CIN, CGIN) = 1-(1-s_{SCC}(CIN))(1-s_{ADC}(CGIN) = 0.91$ for co-infection. The sensitivities are zero for all states, except the CIN- and CGIN-states, see explanation in subsection 3.1.4.

Suppose that the screening ages are $A_s = \{30, 35, \ldots, 60\}$. Since our age is a screening age we perform a screening where we assume that the probability of attending screening is $p_{att} = 0.8$ and the part of the cohort attending screening is therefore $p_{att}F(30)$, while the part that is not attending is naturally $(1-p_{att})F(30)$. Among the attenders we detect precancerous findings

$$T = sp_{att}F(30) = \begin{bmatrix} 0 & 0 & 0.0008 & 0 & 0 & 0 \\ 0 & 0 & 0.0008 & 0 & 0 & 0 \\ 0.00720 & 0.00720 & 0.00728 & 0.00720 & 0.036 & 0 \\ 0 & 0 & 0.0008 & 0 & 0 & 0 \\ 0 & 0 & 0.004 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

These findings are stored at every screening round and are referred to as precancerous findings. They are treated according to the screening scheme and then moved to the recovered compartment. The treated findings are added to recovered states according to the treatment function $\mathcal{T}$ in Equation 3.12 where $(I_{SCC}, CGIN)$, (CIN, I_{ADC}) and $(CIN, CGIN)$ findings are moved to (R, R), since underlying infection automatically also gets treated when any infection is treated. This is followed by moving treated (CIN, x) to (R, x) where $x \in X\backslash\{CIN, I\}$ and equally $(y, CGIN)$ to (y, R) where $y \in X\backslash\{CGIN, I\}$.

The detected part of the cohort becomes a treated cohort,

$$\mathcal{T}T = \begin{bmatrix} 0 & 0 & 0 & 0 & 0.0008 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.0008 & 0 \\ 0.0072 & 0 & 0 & 0.0072 & 0.0553 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The cohort-part that attended screening but where the sensitivity of the screening test was not sufficient to detect the precancers, or where the attenders did not have precancers, is consequently $(1-s)p_{att}F(30)$. The screened cohort is updated by

$$F_{screened}(30) = \mathcal{T}T + (1-s)p_{att}F(30) + (1-p_{att})F(30)$$

and now we can perturb it by the a time step $\Delta t = 1/52$ (1 week), which is the time step we use in the simulation.

Assume that the rates and force of infection parameters are

$$\begin{aligned} &\pi_{I,SCC} = \pi_{I,ADC} = 0.3 && \pi_{CIN} = \pi_{CGIN} = 0.03 \\ &\eta_{I,SCC} = \eta_{I,ADC} = 0.5 && \eta_{CIN} = \eta_{CGIN} = 0.2 \\ &K_{SCC} = 0.12 && K_{ADC} = 0.06 \\ &a_M = 22 && \theta_{SCC} = \theta_{ADC} = 4 \end{aligned}$$

where all rates are expected number of transitions per unit of time, and the time unit is one year. To ease the computations we form two type-specific rate-matrices, where each entry $q(x, y)$ is the transition from state $y \in X$ to state $x \in X$. The matrix takes the

form

$$Q_i(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda(t)_i & 0 & 0 & 0 & 0 & 0 \\ 0 & \pi_{I,i} & 0 & 0 & 0 & 0 \\ 0 & 0 & \pi_j & 0 & 0 & 0 \\ 0 & \eta_{Ii} & \eta_j & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

where $i = SCC$ and $j = CIN$ for squamous cell carcinoma HPV and $i = ADC$ and $j = CGIN$ for adenocarcinoma HPV. Now we can compute the transition probability matrices $N_{\Delta t}^{SCC}$ and $N_{\Delta t}^{ADC}$, using Equation 3.8 and Equation 3.9. The forces of infection computed at this age with Equation 3.1 are $\lambda_{SCC}(30) = 0.0812$ and $\lambda_{ADC}(30) = 0.0406$. We get the probability matrices

$$N_{\Delta t}^{SCC} = \begin{bmatrix} 0.9984 & 0 & 0 & 0 & 0 & 0 \\ 0.0016 & 0.9847 & 0 & 0 & 0 & 0 \\ 0 & 0.0057 & 0.9956 & 0 & 0 & 0 \\ 0 & 0 & 0.0006 & 1.0000 & 0 & 0 \\ 0 & 0.0095 & 0.0038 & 0 & 1.0000 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{bmatrix}$$

and

$$N_{\Delta t}^{ADC} = \begin{bmatrix} 0.9992 & 0 & 0 & 0 & 0 & 0 \\ 0.0008 & 0.9847 & 0 & 0 & 0 & 0 \\ 0 & 0.0057 & 0.9956 & 0 & 0 & 0 \\ 0 & 0 & 0.0006 & 1.0000 & 0 & 0 \\ 0 & 0.0095 & 0.0038 & 0 & 1.0000 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{bmatrix}.$$

We get the time-perturbed cohort

$$F(30+1/52) = N^{SCC}_{\Delta t=1/52}(30) F_{screened}(30) N^{ADC}_{\Delta t=1/52}(30)$$

$$= \begin{bmatrix} 0.1995 & 0.0100 & 0.0092 & 0.0100 & 0.1008 & 0 \\ 0.0102 & 0.0485 & 0.0093 & 0.0099 & 0.0499 & 0 \\ 0.0028 & 0.0030 & 0.0028 & 0.0028 & 0.0143 & 0 \\ 0.0100 & 0.0099 & 0.0092 & 0.0100 & 0.0109 & 0 \\ 0.1572 & 0.0105 & 0.0460 & 0.0173 & 0.2361 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

This computation also served as a control of the MATLAB-computations. Checking that the computations gave the same result as here verified that the time-progression worked as expected.